ARCHIVES of INTERNAL MEDICINE

VOLUME 63 APRIL 1939 NUMBER 4

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TUBERCULOSIS OF THE TONSILS

ITS INCIDENCE AND ORIGIN

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Numerous reports have been made on the incidence of tuberculosis of the tonsils as determined by examination of large series of these organs obtained after tonsillectomies. Such studies have greatest significance when accompanied with a record of the clinical condition of each of the patients concerned, for the incidence varies according to the presence or absence of tuberculosis elsewhere in the body. It is now well known that many, if not most, patients with open pulmonary tuberculosis have tuberculosis of the tonsils. Hence a study of the incidence of tonsillar tuberculosis in a population group including many persons with open pulmonary tuberculosis yields an excessive rate for this disease in the tonsils. Conversely, a slight error is introduced if persons with open tuberculosis of the lungs are excluded, for persons with pulmonary tuberculosis make up not a negligible proportion of the population.

REVIEW OF THE LITERATURE

These facts are readily apparent in a review of the literature on tuberculosis of the tonsils. Newhart, Cohen and van Winkle,[1] in a study of the single sections from tonsils of approximately 100 patients with the adult type of pulmonary tuberculosis, found tuberculosis in 48 per cent. This figure was below the true percentage, for examination of 20 of the "negative" pairs of tonsils by the laborious method

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1. Newhart, H.; Cohen, S. S., and van Winkle, C.: Tonsillectomy in Tuberculosis: Incidence and Pathology of Tuberculosis of the Tonsil in Adults, Ann. Otol., Rhin. & Laryng. **43**:769, 1934.

of serial sections showed a fifth of them to be tuberculous. The indicated high rate was contrasted by the authors with the low rate of 1 per cent found in a study of 100 "healthy" persons. It is significant that the single patient who was responsible for the 1 per cent in this series formerly had pulmonary tuberculosis.

Other studies of this character need not be cited, as the one described is typical. What is most remarkable is that a pathologic state so common is rarely recognized clinically. This is not a reflection on the diagnostic capacity of the physicians examining the throats of tuberculous patients. Tuberculosis of the tonsils is rarely superficial and seldom extensive. Ordinarily it is detectable only on microscopic examination, and when found it is usually submucosal and at the bottom of a crypt. In the clinic at the Henry Phipps Institute approximately 500 patients with active tuberculosis of the adult type are seen annually, all of whom are given careful examinations of the nose and throat, and although the majority of these patients have advanced pulmonary disease and presumably tonsillar tuberculosis also —judging from the figures just recorded—tuberculosis of the tonsils is almost never recognized macroscopically.

The importance of a correlated clinical study is well brought out in the recent report by Urbantschitsch.[2] In examination of 1,000 pairs of tonsils that had been removed because of hypertrophy or other abnormality of the lymphatic structures of the throat, 14 cases of microscopic tuberculosis were found. Roentgen examination of the chests of 13 of the 14 patients concerned revealed obvious or probable tuberculosis of the lungs in almost every one. In 2 advanced pulmonary disease was present, while the rest showed the calcified or fibrotic nodes and nodules of old tuberculosis of the childhood type or the broad shadows of the hilus of the lung and the small infiltrations of still active pulmonary tuberculosis.

It is significant that with the decrease in the incidence of tuberculosis in the general population the incidence of tuberculosis in removed tonsils is also declining. The reports from the University of Michigan, based on an abundance of material, are illuminating in this respect. Weller,[3] in 1921, reported an incidence of 2.5 per cent in 8,697 pairs of tonsils within the preceding thirteen years. Magee,[4]

2. Urbantschitsch, E.: Ueber Tuberkulose des Rachenringes und dessen Erkrankung bei Tuberkulösen, Monatschr. f. Ohrenh. **71**:1096, 1937.

3. Weller, C. V.: The Incidence and Histopathology of Tuberculosis of the Tonsils, Based on Eight Thousand and Six Hundred Tonsillectomies, Arch. Int. Med. **27**:631 (June) 1921.

4. Magee, M. C.: The Changing Incidence of Tuberculosis of the Tonsils, Arch. Int. Med. **59**:445 (March) 1937.

in 1937, brought the study up to date by reporting on 6,359 pairs of tonsils examined in the same laboratory in the intervening years. The incidence had dropped to 0.44 per cent, and the decrease was apparent in all age groups.

From this large volume of material, obtained without deliberate selection with respect to inclusion or exclusion of tonsils from patients with known tuberculosis of other parts of the body, Weller was able to generalize on the source and character of the tonsillar disease. Three types were recognized: (1) focal cryptic tuberculosis, (2) ulcerative and more massive disease and (3) diffuse bilateral follicular involvement. The focal cryptic type was encountered frequently in cases of open pulmonary tuberculosis, and the more extensive ulcerative lesions apparently resulted from massive coalescence of tuberculous tissue of focal cryptic origin. The diffuse form, follicular and usually bilateral, appeared to be merely one expression of generalized tuberculosis after invasion of the blood stream.

In the majority of cases, however, the disease detected was focal, cryptic and monotonsillar. Weller expressed the belief that its character spoke for primary infection, and he noted that it was seen with particular frequency in nurses, hospital interns and advanced medical students—in other words, in a group with more than ordinary exposure to casual tuberculous infection. He pointed out that the figures given on the incidence of tonsillar tuberculosis were probably far below the true incidence, for they were based on examination of single sections, and scars, which might have represented healed tuberculosis, were not included. Weller expressed the opinion that if it were possible to obtain a perfect record of past and present tonsillar tuberculosis the disease would be found as common as the scars of old pleural or pulmonary tuberculosis.

Most investigators who have dealt with the subject have attempted to make a distinction between primary and secondary tuberculosis of the tonsils. Rössner[5] distinguished them logically as follows:

1. Primary: Exogenous, by way of (*a*) inspired air or (*b*) the alimentary canal.

2. Secondary: Endogenous, by way of (*a*) the blood stream, (*b*) the lymph or (*c*) sputum.

Widely varying opinions have been expressed on the comparative frequency of tonsillar infection from these different sources. Rössner herself stated the belief that the tonsillar disease was usually secondary and the result of dissemination by the blood stream from a tuberculous focus elsewhere in the body, and she wrote that this was the view held

5. Rössner, T.: Häufigkeit und Bedeutung der Tonsillentuberkulose, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **135**:214, 1933.

by most authors. Libin and Travushkina,[6] who recently reported on a large series of cases, came to the same conclusion but stated that most authors believe the tonsils of patients with pulmonary tuberculosis become infected through the sputum. These two references are sufficient to indicate the wide difference of opinion.

As indicated before, the question of primary or secondary localization in the tonsils can be settled only in the light of complete knowledge of the condition of the rest of the body, and this degree of knowledge is almost impossible to attain. Hence, although many investigators, like Weller, have considered primary tuberculosis of the tonsils extremely common, proof that such infection is primary is rare. Ghon [7] and his associates in their exhaustive study of the primary focus of tuberculosis concluded that primary tuberculosis of the tonsils is exceedingly infrequent. The requirement for a diagnosis of a primary focus in the tonsil was set as the presence of a typical primary complex, with disease in the tonsil and in the regional lymph nodes and with absence of tuberculosis elsewhere in the body —conditions obviously to be established only by exhaustive postmortem study. In spite of these difficult criteria he was able to cite a few cases. Other cases that appear to satisfy the requirements have been recorded more recently (Suve,[8] Hamperl and Wallis [9]), and in one of these cases [8] infection through a contaminated object, a rubber nipple moistened with sputum, seemed definitely probable.

In spite of the apparent rarity of primary tonsillar tuberculosis, as determined by necropsy, the opinion is still widespread that the tonsils may serve as a portal of entry for tubercle bacilli, and indeed the view once expressed by Aufrecht,[10] that the most important portal of entry for tubercle bacilli in the human body is the tonsil, has not altogether been abandoned. The early views of Behring and Calmette on the portal of entry in tuberculosis are well known. In France especially, owing to the influence of Calmette, the alimentary portal

6. Libin, S. I., and Travushkina, M. V.: Tuberculosis of the Tonsils, Probl. tuberk., 1937, no. 10, p. 67; abstracted, J. A. M. A. **110**:1154 (April 2) 1938.

7. Ghon, A., and Kudlich, H.: Die Eintrittspforten die Infektion vom Standpunkt der pathologische Anatomie, in Engel, S., and von Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930, vol. 1, p. 20.

8. Suve, S. A.: Die Tonsillen als Eintrittspforten für Tuberkelbacillen in Kindesalter, Beitr. z. Klin. d. Tuberk. **82**:279, 1933.

9. Hamperl, H., and Wallis, K.: Ueber primäre Tonsillartuberkulose, Ztschr. f. Hals-, Nasen- u. Ohrenh. **32**:480, 1933.

10. Aufrecht, E.: Die Genese der Lungenphthisie und die Verschiedenheit der mit den Namen Tuberkel bezeichneten Gebilde, Deutsches Arch. f. klin. Med. **75**: 193, 1903.

is stressed. Calmette, Boquet and Nègre [11] pointed with particular emphasis to the possibility of primary absorption of tubercle bacilli from the mouth and pharynx as well as from the intestinal tract.

Montmollin [12] stressed the discoveries in the Lübeck disaster and recalled the well known experiments [13] in which rapid absorption from the tonsils and wide dissemination in the body resulted from experimentally placing minute particles of pigment and other foreign material on the tonsils. Certainly the Lübeck tragedy indicated clearly enough that primary involvement of the tonsillar ring may occur. Of the children dying in this unintentional experiment in massive infection 78 per cent showed the structures of the throat and neck involved (Schürman [14]). The primary infection, it should be noted, was usually multiple, being single in only a few of the infants, and double, triple or quadruple in the rest.

An association between tuberculosis of the tonsils and tuberculosis of the cervical lymph nodes seems clearly established. MacCready and Crowe,[15] while noting tuberculosis of the tonsils in less than 2 per cent of patients without clinical tuberculosis, found lesions in the tonsils in 48 per cent of patients with tuberculous cervical lymphadenitis. Montmollin [12] found tonsillar tuberculosis in 9 of 100 patients from Rollier's sanatorium in Leysin, and in 2 it was associated with disease of the cervical lymph nodes. Schlittler,[16] in 1934, reported tuberculous tonsils in 98 patients with tuberculosis of the cervical lymph nodes. At that time he considered the tonsils the portal of entry, but recently, as a result of study of a second series [17] of 41 patients with tuberculous cervical lymphadenitis, he came to a different conclusion. In every one of the latter the tonsils were tuberculous, and the infection was usually bilateral. As a result of this finding he expressed the belief that the tonsillar disease in both series was hematogenous.

From the foregoing citations it is apparent that the status and the importance of primary tuberculosis of the tonsils are still uncertain.

11. Calmette, A.: L'infection bacillaire et la tuberculose chez l'homme et chez les animaux, ed. 4, revised by A. Boquet and L. Nègre, Paris, Masson & Cie, 1936.

12. de Montmollin, C.: Amygdales et adénoïdes, porte d'entrée de la tuberculose chez l'enfant? Schweiz. med. Wchnschr. **15**:442, 1934.

13. For a review of the experiments mentioned see Weller [3] and Calmette.[11]

14. Schürman, P.: Beobachtungen bei den Lübecker Säuglingstuberkulösen, Beitr. z. Klin. d. Tuberk. **81**:294, 1932.

15. MacCready, P. B., and Crowe, S. J.: Tuberculosis of the Tonsils and Adenoids: A Clinical and Roentgen-Ray Study of Fifty Cases Observed for Five Years After Operation, Am. J. Dis. Child. **27**:113 (Feb.) 1924.

16. Schlittler, E.: Ueber die Bedeutung der Tonsillen als Eintrittspforte der Tuberkulose, Schweiz. med. Wchnschr. **64**:594, 1934.

17. Schlittler, E.: Zur Frage der "primären" Mandeltuberkulose, Schweiz. med. Wchnschr. **68**:42, 1938; abstracted, J. A. M. A. **110**:773 (March 5) 1938.

It is clear that tonsillar involvement secondary to open pulmonary tuberculosis is common, but it is usually a relatively small matter as compared with the pulmonary disease. Tonsillar infection is also common in association with tuberculosis of the cervical lymph nodes, and it would seem most plausible to consider the nodes as involved secondarily to the tonsils, as with any other portal of entry and its tributary lymph nodes. But doubt has been cast on their view.

Finally, slight tuberculosis of the tonsils has been reported as common, and probably representative of primary infection, in persons without clinical evidence of tuberculosis elsewhere. It has been indicated that such infections are prone to heal and to leave little or no local trace. MacCready and Crowe [15] followed a number of patients with such infections over a period of years and came to the conclusion that there is no great likelihood of the development of tuberculosis elsewhere as a result of this entrance of tubercle bacilli.

A number of authors (especially Newhart, Cohen and van Winkle,[1] Rössner,[5] Libin and Travushkina,[6] Schlittler,[17] MacCready and Crowe,[15] Pinkerton [18] and Hudson and Wollaston [19]) have discussed the danger of tonsillectomy in patients with tuberculosis of the tonsils. The general view expressed is that the operation exposes the patient to no undue hazard of spread of the tuberculosis but rather reduces symptoms caused by absorption from tuberculous foci.

It will be seen from the preceding review that two of the most contested problems are (1) whether the small tubercles often found in the tonsils in the absence of demonstrable pulmonary tuberculosis represent primary, or at least exogenous, tuberculosis and (2) whether the tonsillar tuberculosis found so frequently in the presence of pulmonary tuberculosis is hematogenous or is derived from infected sputum.

MATERIAL

The investigation reported here was undertaken in the hope that study of a large number of tonsils removed from children in regions of high tuberculous morbidity and bad hygienic conditions might throw light on these questions. The highest mortality rates for tuberculosis in the United States are said to prevail in the Indian population of the West. Although the officially recorded rate for all Indians in the United States (except for certain agencies not reporting) is given as about 250 per hundred thousand persons (Korns [20]), it is recognized

18. Pinkerton, F. J.: Tonsillectomy in the Tuberculosis Patient, Tr. Am. Laryng., Rhin. & Otol. Soc. **41**:540, 1935.

19. Hudson, B., and Wollaston, F. L.: A Case of Massive Tuberculosis of the Tonsils, Tubercle **17**:30, 1935.

20. Korns, J. H.: Comparative Tuberculosis Findings Among Indians and White Persons in Cattaraugus County, New York, Am. Rev. Tuberc. **34**:550, 1936.

that the official records are often inaccurate, and it is commonly believed that on those reservations where the Indians still follow their more primitive customs the true rate is much higher. The mortality rate for tuberculosis in Montana for the period from 1925 to 1930 has been given as 775 (Warner [21]), with rates as high as 1,300 in some areas (Crouch [22]). An estimate of about 800 was reported recently for one area in the Southwest on the basis of a survey for tuberculosis (Long and Hetherington [23]), and a rate of 409 for the years from 1927 to 1931 was recorded in Minnesota (Burns [24]). Most physicians in the Indian service of the United States would probably consider an estimate of about 600 per hundred thousand conservative for large parts of the western reservations.

Since the physicians in the Indian field service annually perform tonsillectomy on large numbers of patients, it seemed to us that an opportunity was present for studying the question of primary oral infection. By permission of the Office of Indian Affairs and with the cooperation of physicians in the field service, 1,000 pairs of tonsils from Indian children and young adults were secured for examination. More than a third of the specimens were from Navajos. Tuberculosis is common in this tribe, where living conditions are exceptionally primitive, crowding in the home customary, and sputum contamination of the floor and of the household articles frequent. In such conditions buccal infection as well as infection by inhalation might well be expected. The rest of the tonsils were obtained from Blackfeet, Apache, Chippewa, Cherokee, Sioux, Papago, Creek, Paiute and other tribes.

As the study progressed much tonsillar tuberculosis was found, and it seemed wise to collect tonsils from regions with a lower tuberculosis morbidity rate for comparison. The mortality rate for tuberculosis in Puerto Rico, though notoriously high, is much lower than the rates believed to prevail on most Indian reservations, and opportunity was at hand to study tonsils from this source also. Six hundred pairs of tonsils were obtained from patients in three hospitals in San Juan. Finally, through the cooperation of the staffs of the Pennsylvania and the Mount Sinai Hospital, a set of 400 pairs was secured for comparison from Philadelphia, where the mortality from tuberculosis is only slightly higher than that in the United States as a whole. This series, as it turned out, in view of the small amount of tuberculosis found, was

21. Warner, H. J.: The Incidence of Tuberculous Infection Among School Children on Five Montana Indian Reservations, Am. Rev. Tuberc. **26**:507, 1932.

22. Crouch, J. H.: A Study of Tuberculosis Among the Indians in Montana: Preliminary Report, Pub. Health Rep. **47**:1907, 1932.

23. Long, E. R., and Hetherington, H. W.: A Tuberculosis Survey in the Papago Indian Area of Southern Arizona, Am. Rev. Tuberc. **33**:407, 1936.

24. Burns, H. A.: Tuberculosis in the Indian, Am. Rev. Tuberc. **26**:498, 1932.

too small to be of equal statistical significance with the series obtained from the Indian reservations and Puerto Rico.

By original intention the study was limited to tonsils from patients in whom tuberculosis of the lungs was not known to exist, but in the large series from the Indian service a small number of pairs of tonsils from patients known or suspected to have pulmonary tuberculosis were included, and this was true also of a few pairs of tonsils from Puerto Rico.

Blocks of tonsil were fixed in a 5 per cent solution of formaldehyde, and single sections or ribbons of two or three sections were mounted and stained with hematoxylin and eosin. Whenever in the hematoxylin and eosin sections characteristic tubercles were found, stains for acid-fast bacilli were made.

INCIDENCE OF TONSILLAR TUBERCULOSIS

Table 1 summarizes the results for the three groups (as noted, the tonsils of Indians came from widely scattered areas). Tuberculosis

TABLE 1.—*Comparison of the Incidence of Tuberculosis in Tonsils Removed in Communities of Varying Tuberculosis Mortality*

Source of Tonsils	Approximate Tuberculosis Mortality Rate per 100,000 in the Community in 1937	Average Age of Patients, Years	Pairs of Tonsils Examined	Tuberculous Tonsils	
				Number	Per Cent
Indian reservations...	About 600	13.5	1,000	65	6.5
Puerto Rico.....	290	15.9	600	15	2.5
Philadelphia.....	60	12.0	400	1	0.25
Total.....			2,000	81	
Average.....		14.0			4.2

was discovered in one or both tonsils in 81 patients. The rate of tonsillar infection among Indians was by far the highest, that among Philadelphians low, representing only 1 case, while that among Puerto Ricans was intermediate. Only tonsils with tubercles that were histologically characteristic are included in the figures given. Considerable scarring, with good evidence of healing, was found in many of the tonsils showing frank tuberculosis, and similar scarring without definite tuberculosis was occasionally found in other specimens, leading us to suspect a tuberculous origin. The latter specimens, however, are not included as tuberculous in the record.

ORIGIN OF TONSILLAR TUBERCULOSIS

It was obviously impossible to tell from histologic examination of the tonsils whether the infection was primary or secondary, exogenous or endogenous. It was possible, however, to learn something of the

clinical condition of the patients from whom the tuberculous tonsils were obtained. In every case an attempt was made to secure a roentgenogram of the chest. This proved possible in 35 of the 81 cases. In the majority of these 35 cases several weeks, and in some cases a few months, elapsed before the roentgenogram could be secured, as both Indians and Puerto Ricans often returned to distant homes after their brief stay in the hospital and were difficult to locate. In a few cases, fortunately, roentgenograms made just before tonsillectomy was performed were available. These were at hand either through hospital routine or as a sequel to surveys for tuberculosis in the area. Table 2 summarizes the distribution of the 35 cases in which a roentgenogram of the chest was available according to the indicated condition of the lungs.

It is significant that in approximately half the cases (18 of 35) active pulmonary tuberculosis of either the childhood or the adult type was revealed by the roentgenogram. In about two thirds of these

TABLE 2.—*Distribution of Cases of Tonsillar Tuberculosis According to the Condition of the Lungs as Interpreted from Roentgenograms of the Chest*

Condition of Lungs	Cases of Tonsillar Tuberculosis
Apparently normal	9
Calcified primary tuberculosis only	2
Apparently normal, but cervical lymph nodes tuberculous	2
Apparently normal, but spine tuberculous	1
Childhood type of tuberculosis, regressing	3
Childhood type of tuberculosis, active	2
Adult type of tuberculosis, minimal	4
Adult type of tuberculosis, moderately advanced	5
Adult type of tuberculosis, far advanced	7
Total	35

cases, when the tonsils were reported to physicians of the Indian service as tuberculous it was learned that pulmonary tuberculosis had been known or suspected to be present. In the remainder of the 35 cases the discovery of the disease in the tonsils was the first evidence leading to its detection in the lungs. In most of the cases of active pulmonary tuberculosis it is probable that the sputum was positive, either constantly or intermittently, although presumably in the cases of the childhood type and of the adult type of minimal extent the number of bacilli expectorated was small. In the 3 cases of the childhood type in which the lesions were regressing it is possible that the sputum was still positive or had recently been positive for tubercle bacilli, but in the remaining 14 cases the roentgen appearance of the lungs was such as to suggest that they could not have discharged tubercle bacilli. Admittedly, minute lesions might have escaped detection.

In 3 of the 14 cases with sputum presumably negative for tubercle bacilli tuberculosis was known, either from the roentgenogram or from

an accompanying clinical history, to be present in another part of the body. In 2 of these cases, those of tuberculosis of the cervical lymph nodes, a lymphatic connection is obvious, although it was not directly evident in which organ the disease was precedent. This question has already been discussed. In the third case, that of tuberculosis of the spine, the connection might have been through the blood stream or through unrecorded additional tuberculosis in the lymphoid structures close to the tonsils. Subsequent examination did indeed show slight general enlargement of the cervical lymph nodes.

In another 2 of the 14 cases, although there was no evidence of active tuberculosis in the chest, signs of obsolete tuberculosis were present. For the other 9 cases, no record of tuberculosis in any part of the body was obtained, although it is possible that thorough clinical search might have uncovered a tuberculous focus—for instance, in the external lymph nodes—from which hematogenous or lymphogenous spread might have occurred. There is as good reason, however, to consider exogenous infection.

In the absence of any proof to the contrary, therefore, primary tuberculosis of the tonsils must be considered a possibility in the 9 cases in which the roentgenogram of the chest was negative for tuberculosis and in which no tuberculosis was detected in the clinical examination made at the time the roentgenogram was taken. Indeed, it is equally likely that the tuberculosis of the tonsils found in the 2 cases with no other evidence of pulmonary disease than calcified nodules was also primary in the sense that it was exogenous and independent of tuberculosis elsewhere in the body. Although the point is still disputed, there is increasing evidence that such tubercles do not serve as foci for the dissemination of bacilli. Furman's case,[25] recently described, might fall in this group. In all 11 cases the tuberculosis of the tonsils was slight as compared with that seen in the tonsils in cases of known tuberculosis. In most cases it consisted of a few epithelioid tubercles deep in the tonsil; in some cases only a single epithelioid tubercle was found. Among the latter was the case of a girl who originally was thought to have pulmonary tuberculosis and who was kept in the ward of a sanatorium for observation. No pulmonary tuberculosis was found, however, in roentgenograms taken before and after the tonsillectomy. It is possible that this was a case of primary tonsillar infection acquired in a roomful of patients with tuberculosis.

The deep location in the gland, commonly noted, while consonant with hematogenous development of the lesion from an unknown source, is not incompatible with the hypothesis of primary infection. Minor

25. Furman, M. H.: Primary Ulcerative, Infiltrative Tuberculosis of the Tonsils, Ann. Otol., Rhin. & Laryng. **46**:456, 1937.

nontuberculous erosions through which tubercle bacilli could have entered were extremely frequent in the tonsils of this series, and the crypts were usually full of large and small leukocytes which could have carried bacilli into the gland in the course of their wandering.

It is to be noted that the 11 patients who had tonsillar tuberculosis without any other known tuberculosis except the obsolete disease indicated by calcified nodules were much younger than those with tuberculosis of the tonsils in association with active pulmonary tuberculosis. The average age of the former group was 11 years. The average was 17 years in the group with frank tuberculosis of the adult type. This may have no further significance than the fact that an association with open pulmonary tuberculosis could hardly occur before adolescence, because of the relative rarity of this type of disease before that period.

There was little reason on the basis of the histologic lesions observed to believe that the tuberculosis of the tonsils found in association with frank pulmonary tuberculosis of the adult type was hematogenous. Repeatedly the tuberculous process was seen to extend from a number of crypts into the depths of the gland. It could have been argued that this apparent cryptal invasion might in reality be an erosion of the cryptal epithelium by a process extending from below, but the fact that erosion of the rest of the epithelial surface by underlying tubercles was rare made this seem unlikely. Therefore it was believed that the frequent tuberculous involvement of the crypts resulted from without, presumably from sputum that lodged and remained within the crypts. Corroborative evidence was not obtained, however, by finding sputum containing tubercle bacilli within the crypts.

Moreover, a direct test of the hypothesis of origin through sputum by examination of the tonsils of a group of patients with pulmonary tuberculosis whose sputum was supposedly free from bacilli, as determined by repeated examinations, brought out no difference from the group whose sputum contained tubercle bacilli. Through the cooperation of the staff of the Winslow Indian Sanatorium it was possible to examine the tonsils and study the roentgenograms of a group of patients, not recorded in tables 1 and 2, whose sputum had never shown bacilli or had apparently become free from the organisms in the sanatorium either through the application of pneumothorax or through spontaneous favorable progression. Protocols for 5 patients follow.

REPORT OF CASES

CASE 1.—V. L., a Navajo woman 23 years old, had bilateral pulmonary tuberculosis, moderately advanced. Bilateral pneumothorax brought steady improvement. The sputum was positive on Jan. 20, Jan. 27, March 4 and Aug. 31, 1937, and was negative on Dec. 14, Dec. 17, Dec. 18 and Dec. 22, 1937, and on Jan. 18, Feb. 19, Feb. 21, April 4 and May 31, 1938. Tonsillectomy was performed on

April 26, 1938. Extensive tuberculosis of both tonsils was revealed. It may be pertinent to note that when a child this woman had a suppurative cervical lymph node, which had discharged and healed. At the time of the tonsillectomy, however, there was no evidence of active tuberculous disease of the cervical lymph nodes.

Case 2.—K. T., a Paiute man 19 years old, had bilateral pulmonary tuberculosis, moderately advanced. Pneumothorax on the right resulted in steady favorable progression. The sputum was negative on Jan. 1, Feb. 24, April 4 and May 30, 1938. After tonsillectomy on April 13, 1938, both tonsils were found tuberculous. In this case examination of the neck revealed no evidence of past or present tuberculosis of the cervical lymph nodes.

Case 3.—H. A., a Navajo woman 24 years old, had bilateral pulmonary tuberculosis, minimal in extent. Favorable progress was made without pneumothorax. The sputum was negative on Aug. 11, 1937, and on Feb. 14, April 2, May 5, June

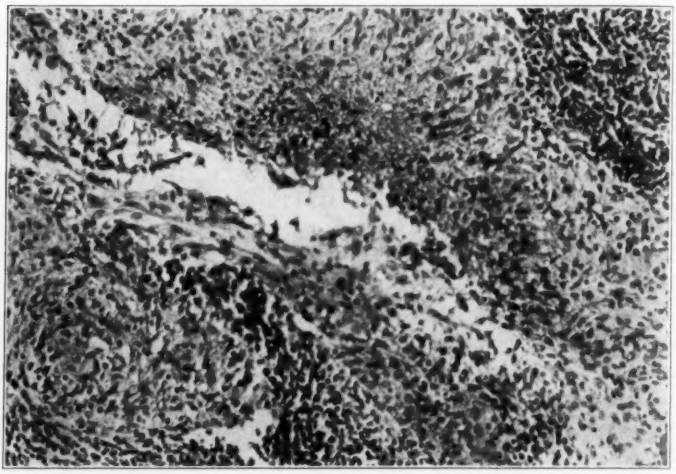

Fig. 1.—Extensive tuberculosis of the margins of a tonsillar crypt in a patient (K. T.) with far advanced pulmonary tuberculosis.

10, June 14 and June 18, 1938; it was positive, with a few bacilli, on June 12, 1938. Tonsillectomy was performed on April 26, 1938. Extensive tuberculosis was seen in both tonsils. There was no evidence, on examination of the neck, of present or past tuberculosis of the cervical lymph nodes.

Case 4.—G. W., a Navajo woman 19 years old, had bilateral pulmonary tuberculosis, minimal in extent. Pneumothorax gave steady slow improvement. There was a history of tubercle bacilli in the sputum during a previous residence in another sanatorium. The sputum was negative on May 5, May 17, May 18, Aug. 26, Aug. 31, Sept. 25 and Sept. 28, 1937, and on Feb. 24, May 4, June 12 and June 14, 1938. After tonsillectomy on April 26, 1938, one tonsil was found tuberculous. On examination of the neck no evidence of past or present tuberculosis of the cervical lymph nodes was found.

CASE 5.—T. S., a Navajo girl 13 years old, had unilateral pulmonary tuberculosis of the childhood type, moderately advanced. There was favorable progression, with scarring. The sputum was negative on April 23, April 24, April 30, May 1, May 3 and Aug. 30, 1937, and on Feb. 1 and April 22, 1938. Tonsillectomy was performed on April 13, 1938; a few tubercles were found in one tonsil. On July 5, 1938, a small grayish white spot was seen on the faucial mucous membrane at the site of the left tonsil, and one lymph node seemed slightly enlarged in the left cervical tissues.

Protocols need not be given for a group of tuberculous patients in the same sanatorium whose cases were studied in connection with the 5 cases just summarized. All of these had positive sputum, and a few had tuberculosis of the cervical lymph nodes. The tonsils of all were tuberculous. It is of interest, however, to note that tuberculosis of the tonsils was not found in 1 case of advanced pulmonary tuberculosis in which the sputum was negative. The protocol follows:

CASE 6.—N. T., a Navajo woman 23 years old, had unilateral pulmonary tuberculosis, moderately advanced, with extensive fibrous pleuritis. Though no collapse of the involved lung was induced, there was steady favorable progression. The sputum was negative on July 22, July 23 and July 30, 1937, and on Feb. 21, March 16, May 4, June 11, June 12 and June 14, 1938. After tonsillectomy on April 26, 1938, no tuberculosis was found in the tonsils. Examination of the cervical tissues on July 5, 1938, revealed nothing abnormal.

It will be evident that this limited study of special cases served only to emphasize the difficulty of demonstrating the route of infection in tuberculosis of the tonsils in cases of pulmonary tuberculosis. It might well be argued that the results speak for the hematogenous or lymphogenous route. On the other hand, examination of sputum by direct smear is far from perfect, and small numbers of bacilli may have been overlooked, although from the long series of negative results recorded it is evident that bacilli were at least rare in the sputum in the cases concerned here. Finally, in some of the cases the sputum was known to have been positive at an earlier stage of the disease, and the tonsillar disease in these cases may have had its origin in that earlier time.

The tuberculosis of the tonsils in the cases of apparent open pulmonary tuberculosis (table 2) was often of wide extent and associated with much scarring, suggesting heavy infection over a long period. This widespread character also argued against explanation of the disease on a hematogenous basis. While tubercle bacilli are known to be commonly present in the blood stream in advanced pulmonary tuberculosis and while evidence of invasion of the blood is frequent in the form of minute tubercles in the liver and spleen in cases in which death occurs from pulmonary tuberculosis, extensive tuberculosis of lymph nodes and viscera, comparable to the extensive tuberculosis found in these tonsils,

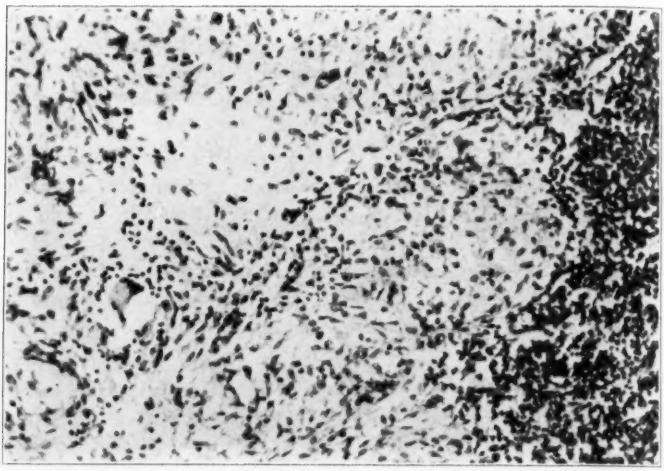

Fig. 2.—Epithelioid and fibroplastic tuberculosis of the tonsil in a patient (M. R.) with pulmonary tuberculosis of minimal but increasing extent.

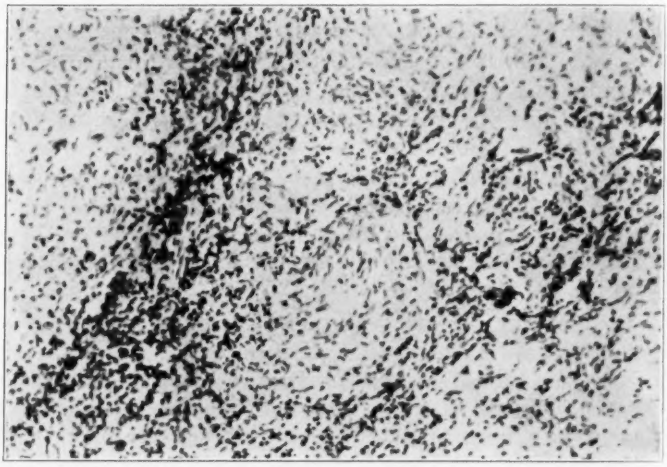

Fig. 3.—Regressing fibroplastic tuberculosis of the tonsil in a patient (S. B.) with chronic tuberculous cervical lymphadenitis.

is rare. The widespread disease of the latter seems more readily explained, therefore, on the basis of frequent infection from bacillus-laden sputum.

In 75 per cent of the cases of tonsillar infection associated with pulmonary tuberculosis believed from the roentgenograms to be open, tuberculosis was discovered in both tonsils, as contrasted with 42 per cent of the total number of cases in which tuberculosis of the tonsils was discovered. As noted previously (Libin and Travushkina [6]), the predominance of bilateral involvement of the tonsils in cases in which there was associated pulmonary tuberculosis has been cited as evidence of a hematogenous source for the tonsillar disease. This seems an unwar-

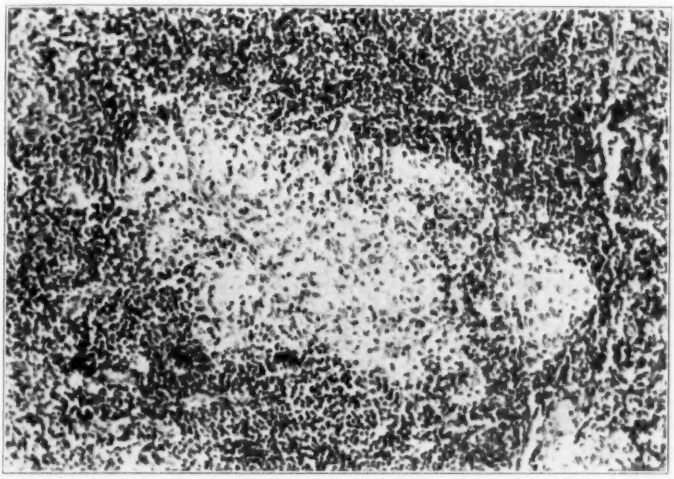

Fig. 4.—Single epithelioid tubercle, probably primary, in the tonsil of a patient (R. P.) with no clinical evidence of tuberculosis elsewhere in the body.

ranted deduction, however, for with the frequent passage of infected sputum through the mouth the opportunity for infection of both tonsils seems excellent.

On the other hand it may be significant that in 80 per cent of the cases of tonsillar infection not associated with tuberculosis elsewhere in the body only one tonsil was found infected. This is further evidence in favor of the view that the infection in these cases may have been primary. First infections are presumably caused as a rule by small numbers of tubercle bacilli as compared with the large numbers commonly present in the total daily output of sputum in cases of open tuberculosis. Correspondingly there would be a better chance for unilateral infection in the former than in the latter. Unilateral involvement

would also seem to point toward primary infection rather than to hematogenous dissemination, in which a fairly even distribution of bacilli over a long period might be expected. This, it will be recalled, is the view adopted by Weller.[8]

These suggestions must, however, be taken in the light of the fact that as a rule only one section of each tonsil was examined. Examination of serial sections or at least many sections from the same tonsil might have uncovered a larger percentage in which the disease was bilateral.

Acid-fast bacilli could be demonstrated in few cases and then only in minute number. This does not cast doubt on the tuberculous nature of the lesions so recorded. The histologic picture was characteristic, in more than half of the cases tuberculosis was present in another part of the body and finally, as is well known, tubercle bacilli are as a rule difficult or impossible to find in the epithelioid tubercles of lymph nodes.

SUMMARY

Two thousand unselected pairs of tonsils from routine tonsillectomies were sectioned and examined microscopically for tuberculosis. One thousand pairs came from various Indian reservations, known to be communities of high tuberculosis morbidity; 600 from Puerto Rico, a region with much tuberculosis, but of lower tuberculosis morbidity than the Indian reservations, and 400 from Philadelphia, a community of low tuberculosis morbidity in comparison with the other two.

Tuberculosis was found in 81 pairs of tonsils, including 6.5 per cent of the tonsils from the Indian reservations, 2.5 per cent of those from Puerto Rico and 0.25 per cent of those from Philadelphia.

Roentgenograms of the chest were secured in the cases of 35 of the 81 pairs. In 16 of these cases active pulmonary tuberculosis of the adult type was found and in 2 active tuberculosis of the childhood type. In general, the tonsillar lesions in this group were cryptal and were more extensive than those in the rest of the 35 cases; on the basis of pathologic appearance the tonsillar tuberculosis was believed to have resulted from direct infection by the bacilli contained in sputum from the associated pulmonary lesion. However, in a small series of cases of "closed" pulmonary tuberculosis in which the sputum was reported negative for tubercle bacilli over a long period and which were examined after the survey of 2,000 cases was completed, tonsillar tuberculosis was regularly found and was usually similar in character to that discovered in a corresponding number of cases in which the sputum was positive. Thus the mechanism of infection of the tonsils in cases of pulmonary tuberculosis remained unproved.

In 3 cases regressing tuberculosis of the childhood type was found in the roentgenogram, and in 3 cases the clinical record indicated that nonpulmonary tuberculosis was present.

In 2 cases the roentgenogram of the chest revealed no abnormality other than calcified nodules from healed tuberculosis of the childhood type. In the remaining 9 cases no tuberculosis was apparent in the roentgenogram of the chest or in the accompanying clinical record. In these 9 cases the tuberculosis of the tonsils was probably primary, and in the 2 in which tonsillar infection was associated with calcified pulmonary lesions it is equally likely that the tonsillar lesion was exogenous. In most of these 11 cases the process consisted of a few epithelioid tubercles, and in 80 per cent of the cases the involvement was unilateral. This is in contrast to the observation in the cases of proved pulmonary tuberculosis, in which the tonsillar lesions were generally extensive and in 75 per cent of cases bilateral.

All stages of regression of tonsillar tuberculosis from active fibroplastic disease to scars indistinguishable from scars of other origin were seen in the series.

The relatively massive tuberculosis of the tonsils in cases of pulmonary tuberculosis, its tendency to be bilateral and its chronicity all point to repeated infection of these organs in the course of the pulmonary disease. Since all studies of tuberculosis of the tonsils show that tonsillar involvement occurs in a large proportion of cases of pulmonary tuberculosis, and since small tubercles tend to regress, there is reason to believe that at some time or other in the course of the disease the great majority of patients with progressive pulmonary tuberculosis, if not all of them, have tuberculosis of the tonsils.

CHRONIC PROGRESSIVE OCCLUSION OF THE INFERIOR VENA CAVA AND THE RENAL AND PORTAL VEINS

WITH THE CLINICAL PICTURE OF THE NEPHROTIC SYNDROME: REPORT OF A CASE, WITH A REVIEW OF THE LITERATURE

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The following case of progressive thrombosis of the inferior vena cava and the renal and portal veins is reported because (1) the condition is exceedingly rare, (2) the patient presented the clinical picture of the nephrotic syndrome and (3) pyelograms taken after intravenous injection of diodrast were suggestive of polycystic disease of the kidneys.

REPORT OF CASE

M. L., 15 year old schoolboy, an American Jew, had a history of measles in 1927 and tonsillectomy in 1928. He entered the hospital on March 9, 1936, because of swelling of the abdomen and the lower extremities. The family history revealed that the boy's father had died of cerebral hemorrhage. The boy had been well until January 1935, when he began to complain of "sour stomach," the attacks being characterized by loss of appetite, nausea, vomiting and belching without pain. The first attack lasted two days. After a symptomless interval of two months there was a recurrence lasting three days. He then enjoyed good health until May 20, when he suffered an attack of nausea and vomiting accompanied by pain in the left costovertebral region and in the lower part of the back lasting three days. On May 31 the costovertebral pain recurred and radiated across the back and over the left side of the abdomen. It was associated with a slight headache, chilly sensations and frequency of urination. Because of the increased severity of the pain and the development of fever the patient was admitted to another hospital on June 1. Examination at that time revealed marked tenderness in the left costovertebral region. The blood pressure was 130 systolic and 90 diastolic. Twenty-eight examinations of the urine showed a specific gravity

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Read at a meeting of the New England Pathological Society, Boston, Nov. 18, 1937.

From the Nephritic Clinic and the Pathology Laboratory of the Beth Israel Hospital and from the Department of Medicine and the Department of Pathology, Harvard Medical School.

ranging from 1.002 to 1.017, with a slight to a very heavy trace of albumin in all specimens. The first specimen was alkaline, and its sediment showed an occasional white blood cell and 20 to 30 red blood cells per high power field. The majority of the remaining urinary sediments revealed no formed elements; several contained from 2 to 25 red blood cells, 1 to 10 white blood cells and many fine granular and hyaline casts per high power field. Gross hematuria was not observed. The red blood cell count on three occasions ranged between 4,510,000 and 5,000,000 per cubic millimeter, with a hemoglobin content of 87 to 95 per cent (Sahli). The white blood cell count on entry was 9,900 per cubic millimeter and one week later was 8,100. The nonprotein nitrogen content of the blood fluctuated between 24 and 32 mg. per hundred cubic centimeters. The total protein content of the plasma was 6.2 and 5.5 Gm., respectively, on two occasions, and the albumin and the globulin content of the serum were 2.3 and 3.9 Gm. per hundred cubic centimeters, respectively. The cholesterol content of the blood on one occasion was 164 mg. per hundred cubic centimeters. The Pirquet reaction (1:1,000) was negative on two occasions. Excretion of phenolsulfonphthalein in one and two hours after intravenous injection of 1 cc. of the dye was 80 and 7 per cent, respectively. An intravenous pyelogram faintly visualized both renal pelves and ureters; the pelves were small, and the calices were elongated and narrowed. The ureters showed no abnormality. A roentgenogram of the chest showed clear pulmonary fields. The temperature fell from 101 F. to normal on the fourth day, and the costovertebral pain on the left rapidly disappeared. At no time was edema noted. The patient lost 13 pounds (5.9 Kg.) in weight. The blood pressure fluctuated between 90 and 130 systolic and 60 and 86 diastolic. The basal metabolic rate was —25 per cent on one occasion. The patient was discharged to the care of his private physician on July 16 with a diagnosis of (?) lipoid nephrosis (without edema) and (?) chronic pyelonephritis.

The patient was well until August 8, when he noticed constant severe pain in the upper portion of the right lower abdominal quadrant, radiating to the right groin and at times to the right costovertebral angle and across to the midepigastrium. There was no nausea, vomiting, diarrhea, urinary symptoms, edema, chills or fever. After taking capsules prescribed by his private physician, the patient noticed redness of the urine the following day. Because of the persistence of the pain in the abdomen and the possibility of acute appendicitis or cholecystitis the patient was referred for the second time to the same hospital. Examination on entry revealed tenderness over McBurney's point and the right upper quadrant, with muscle spasm in both areas, especially marked in the latter. Slight costovertebral tenderness on the right was also noticed. There was no edema. Rectal examination gave negative results. The blood pressure was 110 systolic and 72 diastolic. Thirty-four examinations of the urine revealed a specific gravity ranging from 1.006 to 1.030. All the specimens contained from a trace to a very heavy trace of albumin; many showed up to 3 red blood cells, 1 to 20 white blood cells and 1 to 5 hyaline and granular casts per high power field. Doubly refractile bodies were not observed. The red blood cell count was 3,810,000 per cubic millimeter; the hemoglobin content fluctuated between 80 and 90 per cent (Sahli). The white blood cell count on entry was 9,600 per cubic millimeter, with a polymorphonuclear cell count of 65 per cent. Ten days later the white blood cell count was 16,500 per cubic millimeter. Six days afterward it fell to 11,800. Five determinations of the nonprotein nitrogen content of the blood gave values ranging from 19 to 29 mg. per hundred cubic centimeters. The total protein content of the plasma on entry was 5.2 Gm., the albumin and the globulin content of the serum

being 1.5 and 3.7 Gm. per hundred cubic centimeters, respectively. Three other examinations of the serum showed the total protein content to be 4.8, 4.9 and 4.4 Gm.; the albumin content, 1.2, 1.1 and 1.4 Gm., and the globulin content, 3.6, 3.7 and 3.1 Gm. per hundred cubic centimeters, respectively. The cholesterol content of the blood on entry was 125 mg. per hundred cubic centimeters. The blood pressure fluctuated between 100 and 120 systolic and 60 and 76 diastolic. The basal metabolic rate on two occasions was — 16 and + 2 per cent, respectively.

On the thirteenth day after entry, because of continued pain in the right lower abdominal quadrant and the back and inability to extend the right leg without pain, the patient was transferred to the surgical service with a tentative diagnosis of appendicitis. On August 25 he was taken to the operating room because of the persistent pain in the right lower abdominal quadrant. Just before the operation slight edema and tenderness of the inner side of the right thigh were noted. The operation was postponed, the tenderness and pain subsided on the following day and the patient was transferred back to the medical service with a diagnosis of phlegmasia alba dolens. The right leg became swollen and tender and on August 27 the patient was unable to extend his right leg. Tenderness over the left Poupart ligament, tenderness and spasm in the left lower abdominal quadrant and edema of the upper portion of the right thigh were noted. A diagnosis of chronic nephritis and pelvic phlebitis was made at this time. On September 12 the patient had edema of the legs, scrotum and abdominal wall, with a suggestion of ascites. On September 19 the edema of the legs and scrotum showed considerable increase, but one week later it disappeared almost entirely. The temperature was normal from the day of entry until August 20; from August 21 to 25 it fluctuated between 98 and 100 F.; from August 26 to 30 it was normal; from August 31 to September 2 it fluctuated between 98 and 99 F.; and from September 3 to October 15 it was normal. Before the patient's discharge from the hospital the edema completely disappeared. Prominence of the veins of the abdominal wall was not noted. The patient was discharged to the care of his private physician on October 15, with a diagnosis of (?) chronic nephrosis and the (?) nephrotic stage of chronic nephritis and thrombophlebitis.

The patient did well until two months before admission to the Beth Israel Hospital, when he noticed recurrence of the edema of the legs. About two weeks before entry he became aware of distention of the abdomen. He was told by his private physician that there was fluid in the abdomen and was referred to the hospital. Examination on admission (March 9, 1936) revealed a pale, well developed boy in no acute distress. Ophthalmoscopic examination revealed myopia and temporal pallor of the disks. The heart was of normal size, with normal rhythm and no murmurs. The lungs showed rales at both bases, with diminished breath sounds and absence of tactile fremitus. The abdomen was distended and showed shifting dulness and a fluid wave. The superficial abdominal veins were prominent. There was a slight amount of pitting edema of both lower extremities. The blood pressure was 120 systolic and 95 diastolic. The deep reflexes were normal. Rectal examination gave negative results.

Twelve examinations of the urine revealed a specific gravity ranging as high as 1.038. All the specimens showed from a trace to a heavy trace of albumin; several contained occasional red blood cells, 1 to 5 white blood cells and 1 to 5 hyaline and granular casts per high power field. Doubly refractile bodies were not observed. The red blood cell count on entry was 4,940,000 per cubic millimeter and the hemoglobin value 96 per cent (Sahli). Ten days later these values were 4,400,000 per cubic millimeter and 85 per cent (Sahli), respectively. The white blood cell count was 8,150 per cubic millimeter on entry and 5,800

ten days later. The polymorphonuclear cell count was 65 per cent. One examination of the stool gave negative results. The nonprotein nitrogen content of the blood on two occasions was 37 and 23 mg. per hundred cubic centimeters. The cholesterol content of the blood was 926 and 862 mg. per hundred cubic centimeters. Determinations of the total protein content of the plasma gave values of 3.51, 3.61 and 3.52 Gm., the values for serum albumin being 1.58, 1.51 and 1.53 Gm. and those for serum globulin being 1.93, 2.1 and 1.99 Gm. per hundred cubic centimeters. The Kahn and Hinton reactions of the blood were negative. The basal metabolic rate was —19 per cent.

The patient was given a diet high in protein and low in fat and salt with restricted fluids. His blood pressure fluctuated about an average value of 120 systolic and 84 diastolic. The temperature was normal except on several occasions, when 99 was reached. The patient was free from symptoms except for occasional pain in the midhypogastrium, radiating to the back. His weight fluctuated about 145 pounds (65.8 Kg.) without any change in the edema. Large doses of urea and later of thyroid did not increase the urinary output. On March 26, after nineteen days in the hospital, the patient was discharged to his private physician, with a diagnosis of chronic glomerular nephritis with edema (nephrotic syndrome). He was advised to take a low salt diet, with fluids restricted to 1,200 cc. per twenty-four hours.

On April 20 the patient was readmitted to the Beth Israel Hospital. The interval history revealed that after discharge from the hospital he had remained in bed and the ascites had gradually disappeared in about three weeks. About one week before his second entry he awoke one morning with pain, stiffness and fulness in the right side of the neck. The pain and swelling became worse and were not relieved by alcohol rubs and hot poultices. Two days later the entire right upper extremity was swollen but not painful. The patient was referred to the hospital.

Examination revealed a slightly tender, movable, firm pea-sized mass over the right sternomastoid muscle, with a thickened cord extending downward from the lower border, its course corresponding to that of the external jugular vein. The right upper extremity was swollen, especially the upper portion, with only slight involvement of the hand; venous engorgement was not observed. The infraclavicular and supraclavicular regions were markedly tender. Red streaks along the right arm were not seen. There was no difference in temperature between the two arms. The lungs revealed dulness at both bases, with diminished breath sounds, probably due to the high diaphragm. The heart was not enlarged. The abdomen was distended, and the veins over it and the lower part of the chest were prominent. Shifting dulness and a fluid wave were elicited. The legs showed slight pitting edema. The blood pressure was 118 systolic and 98 diastolic. Thirty-three examinations of the urine revealed a specific gravity ranging from 1.008 to 1.036. All the specimens showed from a slight trace to a trace of albumin. Five specimens contained 1 to 5 red blood cells per high power field. Most of them contained 1 to 15 white blood cells and occasional hyaline and granular casts. Three specimens were loaded with granular and cellular casts. Doubly refractile bodies were seen on only one occasion, on which they were abundant. The red blood cell count varied between 4,600,000 and 5,500,000 per cubic millimeter. The hemoglobin content on several occasions was 85 per cent (Sahli). The white blood cell count on entry was 18,000 per cubic millimeter and fell to 9,900 three days later. Several white blood cell counts taken subsequently revealed variations between 5,000 and 8,000 per cubic millimeter. The polymorphonuclear cell count on entry was 79 per cent. Seventeen days

later it was 60 per cent. The blood smear on two occasions showed abundant platelets and slight achromia of the red blood cells. Two examinations of the stool gave negative results. Four determinations of the nonprotein nitrogen content of the blood showed the highest value to be 35 mg. per hundred cubic centimeters. The sugar content was 74 mg. per hundred cubic centimeters. The cholesterol content on entry was 431 mg. per hundred cubic centimeters; ten and twenty-two days later, it was 520 and 594 mg. respectively. The urea nitrogen content of the blood on two occasions was 13.1 and 10.4 mg. per hundred cubic centimeters. On entry the values for the total protein, the albumin and the globulin content of the serum were 3.99, 1.93 and 2.06 Gm. per hundred cubic centimeters, respectively. Ten days later these values were 4.12, 1.73 and 2.34 Gm., respectively. Thirty-two days after admission the value for serum albumin was 2.1 Gm. and that for serum globulin was 1.79 Gm. per hundred cubic centimeters. The basal metabolic rate on two occasions was — 40 and — 30 per cent, respectively. Roentgen examination of the kidneys showed the renal outlines to be large and regular in contour. Intravenous pyelograms showed the pelves incompletly filled. The calices were well outlined, and the cups were deep. The infundibula were somewhat elongated, "probably owing to polycystic kidneys." The ureters showed no deviation from the normal. There was good excretion of the dye through both kidneys within five minutes after the injection.

The patient was given a high protein, low salt diet, with fluids to 1,500 cc. The temperature, which on entry had been 102.2 F., fell to normal the next day and remained so. The pulse rate fell from 120 to 90 and several days later became normal. The blood pressure remained in the region of 110 systolic and 70 diastolic. The swelling and tenderness of the right side of the neck slowly subsided, as did the swelling of the right upper extremity. The superficial abdominal and the lower thoracic veins were more prominent. The weight on entry was 122½ pounds (55.3 Kg.). There was a gradual increase in weight, 134 pounds (60.8 Kg.) being recorded on the day of discharge. The daily urinary output varied between 1,000 and 1,500 cc. Urea, potassium nitrate and ammonium chloride were ineffective in increasing the volume of urine. On two occasions 2 cc. of salyrgan given intravenously resulted in moderate diuresis. It was noted for the first time that there was evidence of obstruction of the portal vein. On the day of discharge to his private physician (May 31) the patient was up and about and was free from edema of the lower extremities. The abdomen, however, showed signs of fluid. The diagnosis on discharge was: thrombophlebitis of the right external jugular vein, the nephrotic stage of chronic glomerular nephritis and (?) polycystic kidneys. The patient was advised to take a low salt, high caloric, high vitamin, high protein diet, with limitation of fluids to 1,500 cc. per twenty-four hours.

After discharge from the hospital he followed the course prescribed, without any change in his condition.

From July 20 to September 22 he was studied at another hospital. During this period ascites, slight edema of the lower extremities and dilatation of the superficial veins of the upper part of the abdomen and the lower part of the thorax remained unchanged. The blood pressure fluctuated between 106 and 120 systolic and 66 and 80 diastolic. Seven examinations of the urine revealed a specific gravity ranging from 1.018 to 1.031. All the specimens showed from a trace to a heavy trace of albumin. The sediments showed occasional red blood cells, rare to numerous white blood cells and hyaline, granular and cellular casts. On one occasion a few doubly refractile bodies were seen. The red blood cell count varied between 4,830,000 and 5,800,000 per cubic millimeter. The

hemoglobin content fluctuated between 87 and 96 per cent. Three white blood cell counts gave respective value of 6,900, 7,000 and 7,950 per cubic millimeter. Eight determinations of the nonprotein nitrogen content of the blood showed values between 23 and 47 mg. per hundred cubic centimeters. The urea nitrogen content of the blood on two occasions was 14 and 5.5 mg. per hundred cubic centimeters. Nine determinations of the value for the total protein, the albumin and the globulin content of the serum showed the highest values to be 4, 1.21 and 3 Gm. per hundred cubic centimeters, respectively. The cholesterol content of the blood fluctuated between 425 and 800 mg. per hundred cubic centimeters. Numerous tests of the basal metabolism revealed values between —21 and —30 per cent. Roentgen examination of the abdomen showed the kidneys to be larger than normal.

The patient's weight on entry was 132½ pounds (60 Kg.). There was a gradual increase in weight to 142¼ pounds (64.5 Kg.) shortly before his discharge. The daily output of urine varied between 215 and 990 cc. The patient was discharged unimproved to his private physician with recommendations for a high protein, low salt, low acid-ash diet. The diagnosis on discharge was: thrombosis of the portal vein, thrombosis of the renal veins, nephrosis and migrating thrombophlebitis.

The patient was admitted for the third time to the Beth Israel Hospital, on Oct. 2, 1936, because of a severe chill thirty-six hours before, followed by fever and persistent nausea and vomiting. For the twenty-four hours preceding entry the patient suffered from profuse diarrhea. Three days previously the patient and his sister had eaten some meat, and immediately thereafter both complained of nausea, which persisted in the patient. The sister vomited two days and again one day before the patient's entry to the hospital, with complete disappearance of her symptoms. The patient's chill lasted one hour, after which the temperature rose to 104.6 F., gradually falling within the next twenty-four hours to 99 F. About six hours before his admission to the hospital it was still 99 F. Since the onset his breathing had been rapid, and during the few hours before entry he became irrational. The stools were profuse and watery, and he had three or four bowel movements every hour, without gross blood. He complained of pain in the lower portion of the abdomen and in the right groin. The costovertebral region on both sides was tender.

Examination revealed a comatose, dehydrated boy who breathed deeply, rapidly and irregularly. The heart was not enlarged; the cardiac rate was 140 beats per minute. The blood pressure was 78 systolic and 56 diastolic. The lungs revealed a few rales at both bases. The abdomen contained a considerable amount of fluid; the superficial abdominal and the lower thoracic veins were larger than on the previous entry. Tenderness was elicited throughout the abdomen. The edge of the liver was smooth and was felt 2 fingerbreadths below the right costal margin. Brawny edema of the upper part of each thigh was noted. The deep reflexes were equal and active bilaterally.

Examination of the urine revealed a specific gravity of 1.020 and a heavy trace of albumin. The sediment contained 18 to 25 white blood cells, 3 to 6 red blood cells and 1 to 4 granular and cellular casts per high power field. The red blood cell count was 4,450,000 per cubic millimeter, and the hemoglobin value was 80 per cent (Tallqvist). The white blood cell count was 8,500 per cubic millimeter, with a polymorphonuclear cell count of 90 per cent. Examination of the stool failed to reveal occult blood, and microscopic examination showed numerous white blood cells. The nonprotein nitrogen content of the blood was 45 mg. per hundred cubic centimeters, the sugar content was 72 mg., and the

carbon dioxide-combining power was 32.7 volumes per cent. The Kahn and Hinton reactions of the blood were negative. Serum agglutination tests for typhoid bacilli and for paratyphoid bacilli A and B gave negative results.

Shortly after entry the patient lapsed into coma, from which he did not recover. He received intravenous infusions of 5 per cent dextrose and 1 per cent sodium bicarbonate in distilled water and physiologic solution of sodium chloride. The blood pressure rose temporarily to 100 systolic and 70 diastolic but soon fell to 60 systolic and 40 diastolic. The temperature varied between 104 and 106 F. The pulse rate was about 160, and the respiratory rate varied between 40 and 58. He died twenty hours after entry.

Autopsy.—Autopsy was performed three hours after death. Only an abdominal incision was permitted. The peritoneal cavity contained cloudy, straw-colored,

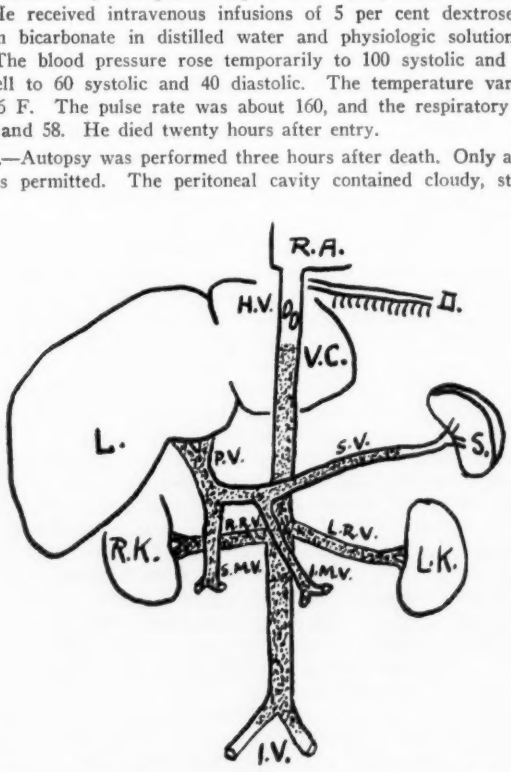

Fig. 1.—Diagram of the thrombosed vessels. *V.C.* indicates inferior vena cava; *P.V.*, portal vein; *S.V.*, splenic vein; *L.R.V.*, left renal vein; *R.R.V.*, right renal vein; *S.M.V.*, superior mesenteric vein; *I.M.V.*, inferior mesenteric vein; *H.V.*, hepatic veins; *I.V.*, iliac veins; *R.A.*, right auricle; *D.*, diaphragm; *L.*, liver; *S.*, spleen; *R.K.*, right kidney, and L.K., left kidney.

thin fluid, a smear of which showed polymorphonuclear leukocytes, lymphocytes and pneumococci. The peritoneal surfaces were smooth, shiny and moist. The foramen of Winslow was closed by filmy adhesions, which were binding down the left lobe of the liver. All the retroperitoneal tissues were thickened, porky and edematous. The mesenteric lymph nodes were small. The pleural cavities contained no free fluid and the pericardial cavity no excess fluid.

Almost the entire inferior vena cava was completely occluded and replaced by a solid cord, about 1 to 1.5 cm. in diameter. The occlusion began at the junction of the common iliac veins (fig. 1) and extended throughout the course

of the inferior vena cava to a point about 2 cm. distal to the entrance of the hepatic veins. Cross section of this solid cord revealed a pale, gray-brown tissue with no lumen. External pressure on this solid cord resulted in the exudation of blood from several small points on the cut surface. When these points were probed they led to a few longitudinal, tortuous channels with narrowed lumens. Both renal veins were similarly occluded from their junction with the inferior vena cava to the hilus of each kidney. The branches of the renal veins were patent, and there were no gross intrarenal thromboses.

A similar type of occlusion was present in the portal venous system, starting at the hilus of the liver but not involving the intrahepatic branches of the portal vein. The portal vein and its tributaries, the splenic vein and the inferior and superior mesenteric veins, were likewise solid cords. The distal portion of the splenic vein near the hilus of the spleen was patent, as were the distal

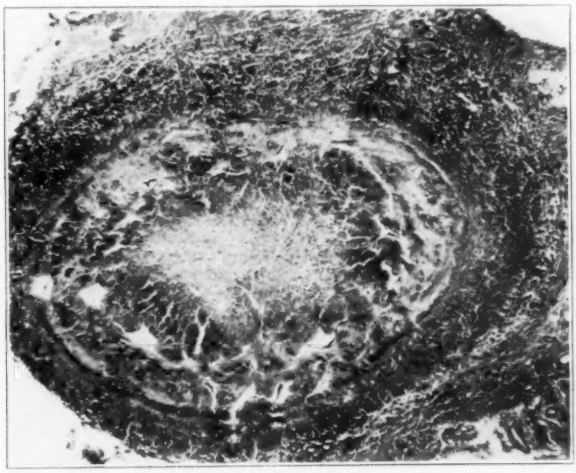

Fig. 2.—Transverse section (× 30) of the inferior vena cava, showing complete thrombosis with recanalization.

branches of both mesenteric veins. The azygos and the superficial epigastric veins were dilated. The restricted incision precluded proper study of the system of the superior vena cava.

Microscopically a similar picture was observed in the inferior vena cava, the renal veins, the portal vein and its branches and also the peritracheal veins (figs. 2 to 6). The lumens of all these vessels were obliterated in all regions by thrombi of various ages. For the most part these lumens were replaced by a network of tortuous, endothelium-lined, sinusoid-like channels, the total cross section of which was much smaller than the original channel. The original wall, with its muscular media, was still generally recognizable. No intima was present. It was replaced throughout by a rather loose fibrous tissue continuous with that in the broad trabeculae separating the sinusoidal channels. Only occasionally in these trabeculae were there small collections of hemosiderin-laden monocytes. More rarely even a scattering of lymphocytes was seen in this

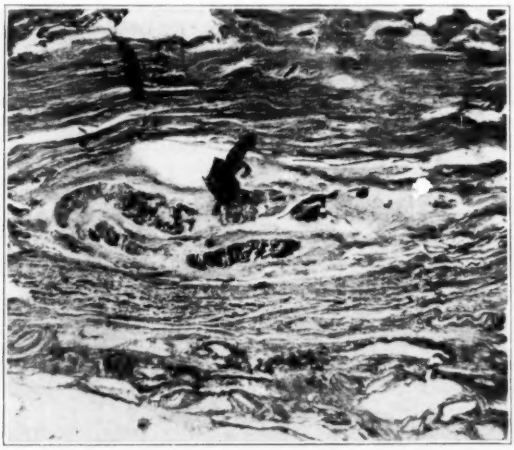

Fig. 3.—Longitudinal section (× 20) of the inferior cava, showing the recanalized thrombus with fresh thrombi in many of the smaller venous channels.

Fig. 4.—Longitudinal section (× 30) through the portal vein, showing the recanalized thrombus.

Fig. 5.—Section (× 30) through the renal vein, showing the recanalized thrombus and numerous smaller venous channels containing fresh thrombi.

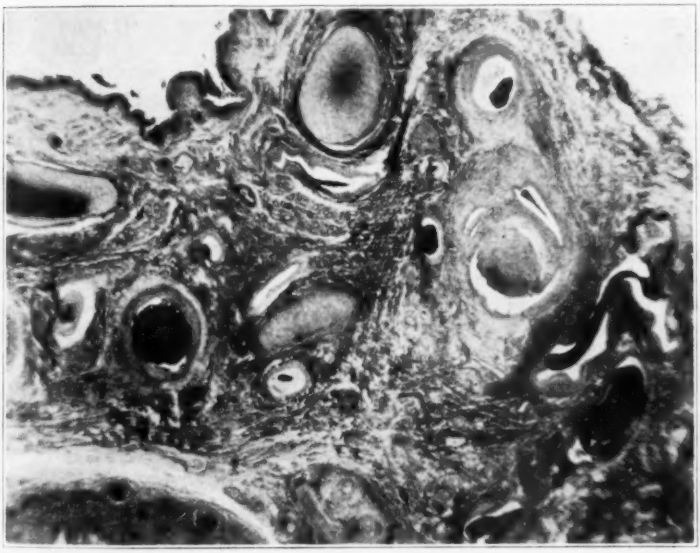

Fig. 6.—Section (× 30) of the trachea, showing the recanalized thrombosed veins, some of which contain fresh thrombi.

region. An occasional collection of fat-laden monocytes was also present, especially in the portal vein. Besides this picture of an old healed process there was evidence that the mechanism leading to occlusion was still active.

In all the sections from the occluded veins there were small fresh thrombi forming in some of the sinusoidal spaces. Rarely did such a thrombus fill the space. Usually it was attached to the wall at only one point. It consisted largely of fused platelet strands, fibrin fibrils or fused fibrin or a mixture of these ingredients. Entangled blood cells were uncommon. Invasion and organization by fibroblasts growing out from the point of attachment comprised the usual picture. Often a knot of fused hyaline material was present in the midst of a projection into a sinusoid, obviously a small, almost organized, recently formed thrombus.

The heart weighed 240 Gm. and showed no abnormality of the myocardium or endocardium. A few petechial hemorrhages were present in the epicardium. The coronary arteries showed no disease. The abdominal aorta was only 4 cm. in diameter, and there were several scattered arteriosclerotic plaques.

The kidneys were large, each weighing 360 Gm. Their capusles were not thickened and were easily stripped, revealing smooth, shiny, bluish red, congested surfaces. The cut surfaces were smooth and showed distinct markings throughout. The cortex was everywhere sharply differentiated from the medulla, had a thickness of 0.8 cm. and was uniformly bluish red with an occasional yellowish area, especially at the upper poles. The medulla of the kidneys was pale red with a characteristic yellowish tinge. The amount of pelvic fat was not increased. The pelves were not dilated, and the calices revealed smooth and shiny mucosa.

Microscopically the glomeruli were of normal size, without any degeneration or proliferation of the epithelium or endothelium (fig. 7). The capillary tufts were unobstructed and did not contain any polymorphonuclear leukocytes. Droplets of fat in the glomeruli were not demonstrated with the scarlet red stain. The tubular epithelium showed slight cloudy swelling (fig. 8). Many tubules contained granular débris without any cellular elements. The scarlet red stain revealed a rare droplet of fat in the tubular epithelium. Doubly refractile bodies were not seen. There was no structural change in the arterioles and arteries. Intrarenal venous thrombosis was observed in one spot only. The interstitial tissue was edematous and contained an occasional focus of round cells. Sections stained by the McGregor technic[1] revealed no thickening of Bowman's capsule or of the glomerular basement membrane (fig. 9). No intracapillary fibrin or hyaline fibers were seen.

The liver weighed 1,960 Gm. and was grossly normal except for congestion. Microscopic examination revealed cloudy swelling, marked congestion and dilatation of the sinusoids and dilatation of the central veins without necrosis of the hepatic cells. There was no suggestion of cirrhosis.

The spleen weighed 370 Gm. and was not remarkable on gross or microscopic examination. Culture gave negative results.

The rest of the viscera were normal except for slight diffuse fibrosis of the alveolar walls of the lungs and congestion and edema of the intestines.

Summary of the Case.—A 15 year old schoolboy, an American Jew, began to suffer from attacks of nausea, vomiting and anorexia twenty-two months before

1. McGregor, L.: The Finer Histology of the Normal Glomerulus, Am. J. Path. **6**:545, 1929; The Cytological Changes Occurring in the Glomerulus of Clinical Glomerulonephritis, ibid. **6**:559, 1929.

his first admission to the hospital. Five months later he had an attack of costovertebral pain on the left, which was diagnosed as due to pyleonephritis and nephrosis. One month later he had pain in the right lower abdominal quadrant, radiating to the right groin, to the costovertebral region on the right and across to the midepigastrium, accompanied by spasm and tenderness in the right abdominal quadrants. There were edema and tenderness of the inner side of the right thigh, followed by edema of both legs, the scrotum and the abdominal wall and tenderness and spasm over the left lower abdominal quadrant. The edema disappeared several weeks later. Nine months before his admission to the hospital, edema of the legs occurred, followed by swelling of the abdomen. Three months later he had thrombophlebitis of the right external jugular vein and questionable similar involvement of the right subclavian vein. Prominent veins of the

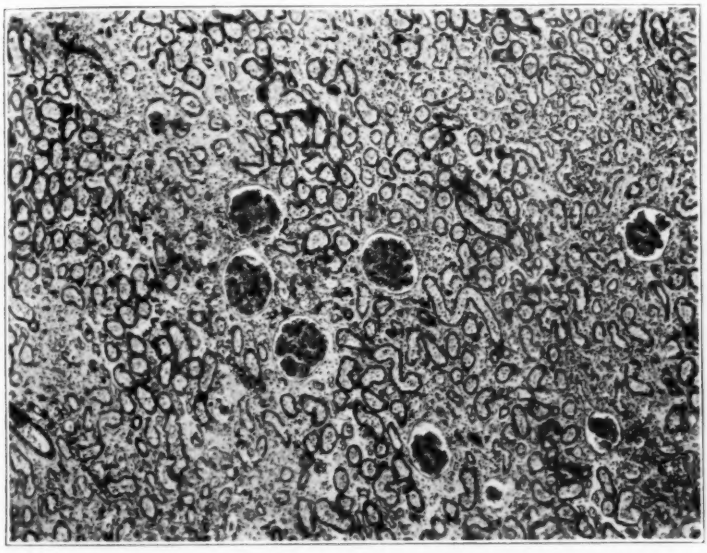

Fig. 7.—Section (× 50) of the kidney, showing interstitial edema.

abdominal wall and the lower part of the thoracic wall appeared. Three days before entry the boy had chills, fever, nausea and vomiting, followed by severe diarrhea, coma and death. Physical examination gave negative results except for distention of the abdomen with fluid, prominent superficial veins of the abdomen and the lower anterior portion of the chest and slight pitting edema of the legs. The blood pressure was normal throughout the illness. Laboratory examinations revealed no anemia or impairment of renal function; there were massive albuminuria; a few red and white blood cells, casts and doubly refractile bodies in the urinary sediment; hypercholesteremia and hypoproteinemia, with reversal of the albumin-globulin ratio (table).

Postmortem examination revealed pneumococcic peritonitis, enlarged and swollen kidneys and old recanalized and fresh fibrin thrombi in the inferior vena

Date 1935	Urinalysis* Number of Examinations	Specific Gravity	Albumin†	Formed Elements After Centrifugation (Per High Power Field) Casts	White Blood Cells	Red Blood Cells	Doubly Refractile Bodies	Blood Chemistry Total Protein, Gm. per 100 Cc.	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.
January	..	.....	.....	.....	....	....	.....	....	....	....	...	..	...	..
March	..	.....	.....	.....	....	....	.....	....	....	....	...	..	..	..
May 20	..	.....	.....	.....	....	....	.....	....	....	....	...	..	...	..
May 31	..	.....	.....	.....	....	....	.....	....	....	....	...	..	..	..
June 1 to July 16	28	1.002 to 1.017	S.T. to V.H.T.	0 to many hyaline and coarse brown granular	0-10	0-25	0	6.20 5.50	2.30	3.90	164	..	30 27 27 32 24 29 32 29	..
Aug. 12 to Oct. 15	34	1.006 to 1.030	T. to V.H.T.	1 to 5 hyaline and granular	1-20	0-3	0	5.20 4.80 4.90 4.40	1.50 1.20 1.10 1.40	3.70 3.60 3.70 3.10	... 125	..	29 27 25 27 19	..
1936														
March 9 to March 28	12	1.020 to 1.038	T. to H.T.	0 to 1 hyaline and 0 to 5 granular	0-5	0-1	0	3.51 3.61 3.52	1.58 1.51 1.53	1.93 2.10 1.99	920 862	..	37 23	..
April 21 to May 31	29	1.008 to 1.036	S.T. to T.	0 to 1 hyaline, 0 to loaded granular and cellular	0-25	0-5	+	.... 3.99 4.12	.... 1.98 1.73 2.10	.... 2.06 2.34 1.79	431 520 446 594	.. 13 10	31 35 31 32	.. 74
July 20 to Sept. 22	7	1.018 to 1.031	0.5 to 2.0%	Rare to numerous hyaline, granular and cellular	Rare to numerous	Rare	+	2.70 2.40 2.10 3.35 3.80 4.00 3.49 3.65 2.63	0.81 0.60 0.75 0.78 1.00 1.00 1.21 1.06 1.13	1.89 1.80 1.35 2.57 2.80 3.00 2.28 2.59 1.50	690 516 445 425 571 640 800 709 800	.. 14 5.5	27.3 27 28.1 42 23 47 28.6 29.1	..
Oct. 2 to Oct. 3	1	1.020	H.T.	1 to 4 granular and cellular	18-25	3-6	..	....	....	....	327	..	45	72

† Heller's ring test (read after 1 minute). S.P.T. indicates slightest possible trace; V.S.T., very slight trace.
* Benedict's qualitative test for sugar gave a negative reaction in all specimens of urine.

Hematologic Picture			Blood Pressure, Mm. Hg		Basal Metabolic Rate, per Cent	Symptoms	Probable Venous Lesions	Edema	Collateral Circulation
Hemoglobin, per Cent	Red Blood Cells, Millions	White Blood Cells	Systolic	Diastolic					
...	....	.....	.....	.....	....	"Sour stomach"			
...	....	.....	.....	.....	....	"Sour stomach"			
...	....	.....	.....	.....	....	Nausea and vomiting; pain in costovertebral region and back (3 days)			
...	....	.....	.....	.....	....	Costovertebral pain on left; frequency of urination	Thrombosis of left renal vein		
90 95 92	4.51 5.00 4.55	9,900 8,100	90-130	60-86	—25	Subsidence of pain and urinary symptoms	.....	0	
80 85 90	.... 3.81	9,600 16,500 11,800	..... 100 to 120	 60-70	.... —16 + 2	Pain in right lower abdominal quadrant radiating to right costovertebral region and mid-epigastrium; costovertebral tenderness on right	Thrombosis of right renal vein; pelvic phlebitis; thrombosis of inferior vena cava and portal vein	Thighs, legs, scrotum and abdominal wall	
90 96 85	4.94 4.95 4.44	8,150 5,800	 120	 84	.... —19	Recurrent edema of legs; ascites; occasional pain in hypogastrium radiating to back	.....	Legs; ascites	Prominent veins in abdominal wall
85 85 70 75 85	5.00 4.65 4.60 4.90 5.50	18,000 9,900 10,700 5,000 9,800 8,500 8,000	 110	 70	.... —40 —30	Pain and fulness in right side of neck; swelling of right arm	Phlebitis of right external jugular and (?) right subclavian veins	Legs; ascites	Prominent veins in abdominal wall and lower anterior part of thorax
96 87 87 88 89 92 88 94	5.80 4.86 4.96 4.83 5.04 5.57 4.96 5.21	..... 6,900 ..... 7,000 7,950	..... 106 to 120	..... 66 to 80	—21 —24 —25 —28 —27 —29 —30 —29.5 —26.4 —26	.....	.....	Thighs and legs; ascites	Dilatation of superficial veins of upper portion of abdomen and lower portion of anterior thorax
80	4.45	8,500	70-100	40-70	....	Gastroenteritis	.....	Thighs; ascites	Prominent veins in abdominal wall and lower anterior portion of thorax

ST., slight trace; T, trace; H.T., heavy trace; V.H.T., very heavy trace.

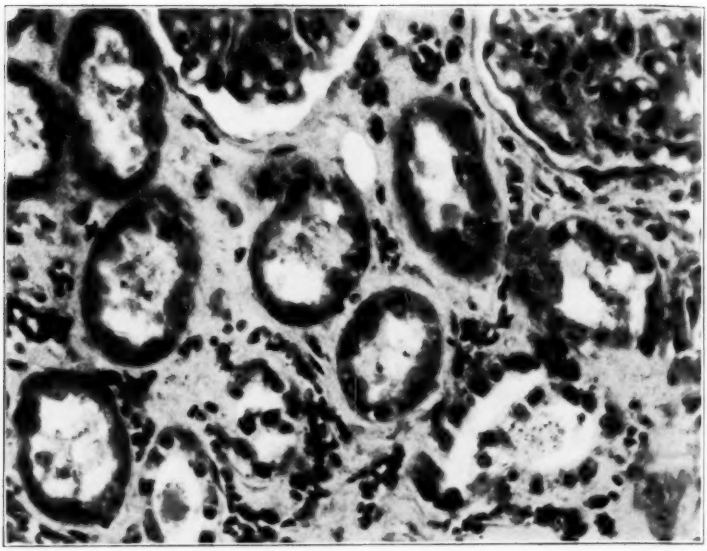

Fig. 8.—Section (× 200) of the kidney, showing slight cloudy swelling of the tubular epithelium. The interstitial tissue is edematous.

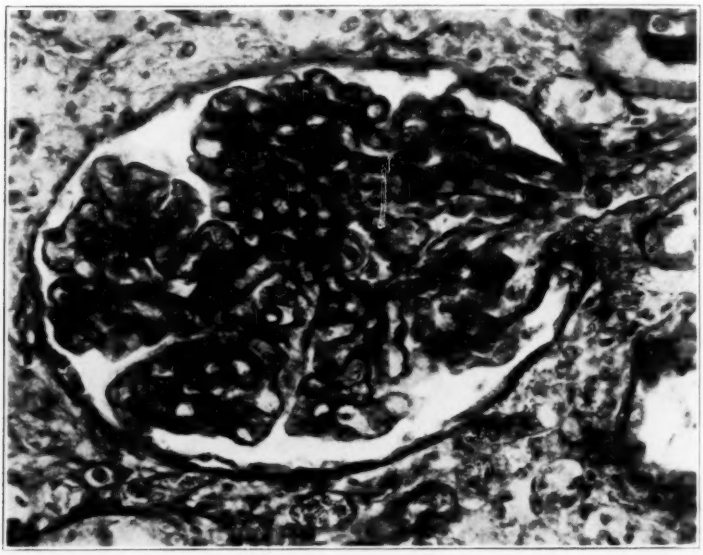

Fig. 9.—Section (× 400) of the kidney, stained by the McGregor technic, showing a normal glomerulus.

cava, the peritracheal, portal, splenic and renal veins and the proximal portions of the mesenteric veins. Microscopic examination of the kidneys revealed no abnormality of the glomerular epithelium, endothelium or basement membrane. The tubules showed slight cloudy swelling and no doubly refractile bodies. The interstitial tissue was edematous. The heart, lungs, liver, spleen and pancreas were normal on gross and microscopic examination.

REVIEW OF LITERATURE

The literature dealing with venous thrombosis is extensive. The important features applicable to this case are herewith presented:

Thrombosis of the Portal Vein.—The clinical picture and pathologic anatomy of this condition have recently been thoroughly reviewed by Simonds [2] and need not be discussed at this point except to state that the manifestations of thrombosis of the portal vein in our case were ascites, collateral circulation and abdominal pain. Hematemesis and a palpable spleen were not present. Simonds found that the most common causes of death were hemorrhage and intestinal infarction. Our patient died of pneumococcic peritonitis. Cases of thrombosis of the portal vein associated with other venous thromboses or with nephrosis were not mentioned by Simonds [2] or by Weir and Beaver.[3]

Thrombosis of the Inferior Vena Cava.—The clinical picture and pathologic anatomy of this condition have been adequately described by many observers.[4] The two important signs of thrombosis of the inferior vena cava are edema of the lower extremities and the development of a characteristic collateral circulation. It is not well recognized that slow occlusion is compatible with a long life. The presence or absence of albuminuria helps to determine the location of the thrombosis; if present, it indicates thrombosis above the entrance of the renal veins, and if absent, it indicates thrombosis below the entrance of the renal veins. During the course of his illness our patient had edema of the lower extremities but the collateral circulation was typical of thrombosis of the portal vein.

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2. Simonds, J. P.: Chronic Occlusion of the Portal Vein, Arch. Surg. **33**: 397 (Sept.) 1936.

3. Weir, J. F., and Beaver, D. C.: Diseases of the Portal Vein: A Review of One Hundred and Twenty-Seven Cases, Am. J. Digest. Dis. & Nutrition **1**:498, 1934.

4. (*a*) Blumer, G.: Thrombosis of the Inferior Vena Cava, in Osler, W.: Modern Medicine, Philadelphia, Lea & Febiger, 1907, vol. 4, p. 529. (*b*) Heilmeyer, L., and Lippross, O.: Ueber doppelseitige Nierenvenenthrombose bei Erwachsenen, Deutsches Arch. f. klin. Med. **179**:80, 1936. (*c*) Osler, W.: Case of Obliteration of Inferior Vena Cava with Great Stenosis of the Orifices of the Hepatic Veins, J. Anat. & Physiol. **13**:291, 1878-1879.

Thrombosis of the Renal Veins.—Acute primary thrombosis of the renal veins is rare in adults but more common in infants.[5] The clinical features are albuminuria, bloody urine, oliguria, palpable kidneys which grow larger under observation, uremia and death. Hemorrhagic infarction, with extensive thrombosis of the renal veins extending into their smaller radicles, is usually present. In some cases the infarction is attributed to multiple capillary thromboses and less extensive thrombosis of the renal veins.

Chronic glomerular nephritis, amyloid disease, pyelonephritis or eclampsia may present an acute terminal picture of uremia owing to the presence of multiple thrombi in the main and medium-sized branches of the renal veins, which results in the picture of infarction and necrosis of the kidneys.[6]

Thrombosis of the renal veins may develop from the intravenous extension of thrombophlebitis of the inferior vena cava or phlebitis of the leg or the pelvic organs.[7] If the involvement is unilateral the condition may be amenable to surgical intervention.[8]

Cases of thrombosis of the renal veins caused by extension from a renal or an adrenal tumor or compression by a retroperitoneal neoplasm or an aneurysm have been reported.[9]

The experimental production of acute (bilateral and unilateral) thrombosis of the renal veins has been carried out by many investigators.[10]

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5. Welch, W. H.: Thrombosis, in Allbutt, T. C.: System of Medicine, New York, Macmillan & Company, 1899, vol. 6, p. 170. Aschner, P. W.: Thrombosis and Thrombophlebitis of the Renal Veins, J. Urol. **17**:309, 1927. Oppenheim, F.: Ueber den hämorrhagischen Niereninfarkt der Säuglinge: Ein anatomischer Beitrag zu dem Kapitel der toxischen Capillarwandschadigung, Ztschr. f. Kinderh. **26**:192, 1920.

6. Petremand, S.: Beitrag zur Kenntnis der Nierenvenenthrombose bei Säuglingen, Klin. Wchnschr. **2**:2244, 1923. Herzog, G.: Ueber hyaline Thrombose der kleinen Nierengefässe und einen Fall von Thrombose der Nierenvene, Beitr. z. path. Anat. u. z. allg. Path. **56**:175, 1913. Neu, J.: Ueber doppelzeitigen Nierenvenen Thrombose, Klin. Wchnschr. **1**:2001, 1922. Opsahl, R.: Pathology of Amyloid Kidney in Connection with Four Cases, Norsk mag. f. lægevidensk. **97**: 1028, 1936. Blumer.[4a] Heilmeyer and Lippross.[4b]

7. Reese, H.: Zur Symptomatologie der Nierenvenen Thrombose, Deutsches Arch. f. klin. Med. **78**:588, 1903.

8. Ehrström, R.: Die klinik der Niereninfarkte und der Nierenvenenthrombose, Acta med. Scandinav. **83**:458, 1934. Marion, G.: Necrose du rein droit par thrombose de la veine renale nephrectomie; guérison, J. d'urol. **15**:455, 1923.

9. Hyman, A.: Clinical and Surgical Aspects of Renal Neoplasms, Surg., Gynec. & Obst. **41**:308, 1925.

10. (*a*) Harrington, S. W.: The Effect on the Kidney of Various Surgical Procedures on the Blood Supply, Capsule and on the Ureters, Arch. Surg. **2**:547 (May) 1921. (*b*) Rowntree, L. G.; Fitz, R., and Geraghty, J. T.: The Effects of Experimental Chronic Passive Congestion on Renal Function, Arch. Int. Med. **11**:121 (Feb.) 1913.

The clinical picture and pathologic anatomy of chronic thrombosis of the renal veins are not well known. Acute unilateral thrombosis of the renal vein may progress to a chronic stage after the initial hematuria and enlargement and tenderness of the kidney subside. Albuminuria may persist for months.[7] Gradual and progressive to complete obstruction of the renal vein, as produced by Rowntree [10b] in unilaterally nephrectomized dogs, resulted in albuminuria, normal renal function and the development of a collateral circulation involving the capsular, lumbar, ovarian and adrenal veins. Histologic studies of these kidneys were not reported. From the sequence of the symptoms in our case, thrombosis of the right renal vein presumably developed about ten weeks after a similar process had occurred in the left renal vein. The interval probably permitted an adequate collateral venous circulation from the left kidney to develop, so that acute renal failure did not follow the later occlusion of the right renal vein.

Thrombosis of the Inferior Vena Cava and the Portal and Renal Veins.—Weber [11] and Shattock [12] reported cases of acute and chronic thrombosis of the inferior vena cava and the renal veins. Shattock's report revealed the unusual history of a 24 year old medical student who had severe pain in the lumbar portion of the spine after running a race. Edema of the legs and the lower part of the trunk supervened and was followed by progressive enlargement of the superficial veins of the abdomen. Albuminuria appeared at once and persisted throughout life. Death occurred twenty-five years later, the patient having carried on an active obstetric practice. Postmortem examination revealed the inferior vena cava to be converted into a flat, impervious ribbon extending from the point of entry of the hepatic veins downward below the renal veins. The latter were closed at their entrance to the inferior vena cava. The return of blood from the kidneys probably took place through the veins of the renal capsules, the lumbar veins and the azygos veins. The portal vein was not described. Microscopic studies were not made.

Careful search of the literature revealed only 1 reported case of thrombosis of the inferior vena cava and the portal vein.[13] The patient at the age of 34 had diffuse abdominal pain, most severe in the left hypochondrium, followed by fever, vomiting, anuria and transitory

11. Weber, F. P.: Thrombosis of Inferior Vena Cava and Both Renal Veins, Internat. Clin. **3**:132, 1921; Thrombosis of Inferior Vena Cava and Both Renal Veins, Proc. Roy. Soc. Med. (Sect. Med.) **14**:9, 1921.

12. Shattock, S. G.: Occlusion of the Inferior Vena Cava as a Result of Internal Trauma, Proc. Roy. Soc. Med. (Path. Sect.) **6**:126, 1913.

13. Lutembacher, R.: Thrombo-phlébite de la veine cave inférieure et de la veine porte, Presse méd. **43**:1175, 1935.

albuminuria. Edema and ascites supervened and slowly disappeared over a period of fifteen to eighteen months as the collateral circulation developed. The author's excellent photographs show the extensive dilatation of the superficial veins of the groin, abdomen, and thorax. During the remaining fifteen months of his life the patient suffered from several attacks of abdominal pain. The cause of death was said to be hepatorenal insufficiency. Postmortem examination revealed old thrombosis of the inferior vena cava, extending from the bifurcation to the entrance of the hepatic veins, and more recent thrombosis of the portal vein. The renal veins were permeable. An adherent thrombus in the right renal vein extended into the inferior vena cava. The kidneys were large and showed on microscopic examination diffuse and complete degeneration of the tubular epithelium. It was felt that the tubular degeneration developed shortly before death. The liver was of normal size; its surface was nodular. Cut sections had an appearance typical of Laënnec's cirrhosis. Microscopic examination revealed marked portal cirrhosis. The weight of the spleen was not given, but the organ measured 14 by 10 cm.

The case is unusual because of the spontaneous absorption of the edema and ascites brought about by the collateral circulation and the adequate renal function due to the permeability of the renal, lumbar and azygos veins.

Thrombophlebitis Migrans.—The clinical picture and pathologic anatomy of this rare condition have been recently reviewed by Stern.[14] Thrombophlebitis migrans is characterized by phlebitis and often by thromboses involving long or short segments of deep or superficial veins. The migration from vein to vein and the subsidence of the process in one location and its appearance in another are distinctive features of this condition. Any organ may be affected, so that the patient may recover in several weeks or may die from the effects of the thrombotic lesions. Unless one of the superficial veins is involved at some time during the illness it is difficult to make a diagnosis of thrombophlebitis migrans. Arterial phenomena, which are outstanding features in Buerger's disease,[15] do not constitute a part of this entity. Of the 40 patients reported on in the literature, as reviewed by Stern, none showed thrombosis of the inferior vena cava and the portal and renal veins or presented the nephrotic syndrome clinically.

14. Stern, N. S.: Thrombophlebitis Migrans, South. M. J. **27**:849, 1934.

15. Buerger, L.: The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924.

Progressive thrombosis of the veins, as described by Karsner,[16] is probably the same entity as thrombophlebitis migrans. In his book entitled "Human Pathology" Karsner stated:

> Chronic phlebitis may constitute a part of that rare disease sometimes spoken of as progressive thrombosis of the veins. Trauma or some unknown condition may establish thrombosis in any vein of the body. Subsequently, other veins become involved, usually not by direct extension, until a number of chronic thrombi may be established in various situations.

Karsner observed 1 patient clinically, the illness beginning at the age of 30 and progressing over a period of more than twenty years. It was characterized by recurrent phlebitis of the superficial veins of the lower extremities. Visceral involvement was not noted.[17]

Collateral Circulation.—The superficial collateral circulation in our case was characteristic of that associated with thrombosis of the portal vein, i. e., the superficial veins on the surface of the abdomen were near the median line of the lower part of the thorax and over the anterior portion of the abdominal wall between the xiphoid process and the symphysis pubis, with slight prominence around the umbilicus. The prominent superficial veins in the iliac and inguinal regions and along the lateral aspect of the lower part of the abdomen and the thorax observed in cases of obstruction of the inferior vena cava were not present.

Roentgenographic Appearance of Kidneys in Chronic Thrombosis of the Renal Veins.—Pyelographic examination in our case revealed good excretion and concentration of the diodrast within five minutes after injection. Elongation and pressure defects of the calices and pelves were noted (fig. 10). The kidneys were enlarged and were regular in contour. Over a period of almost a year further increase in the size of the kidneys was observed by measurement of the distance between the upper and the lower pole of each kidney:

	Right Kidney	Left Kidney
6/25/35	14.2 cm.	13.6 cm.
5/13/36	15.5 cm.	15.1 cm.

The deformity of the calices and pelves resembled that caused by polycystic disease of the kidneys.[18] In our case, however, only edema of the interstitial tissue was present to explain the roentgenologic changes.

Nephrotic Syndrome.—Albuminuria, cholesteroluria, slight hematuria, edema, hypoproteinemia, reversal of the albumin-globulin ratio,

16. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, 1926, p. 475.

17. Karsner, H. T.: Personal communication to the authors.

18. Macalpine, J. B.: Cystoscopy and Urography, Baltimore, William Wood & Company, 1936, p. 414.

hypercholesteremia and absence of hypertension and of impaired renal function are regarded as criteria of the nephrotic syndrome.[19] The present case closely fulfils these clinical criteria, although none of the usual causes of the nephrotic syndrome, i. e., glomerular nephritis, amyloid disease or lipoid nephrosis, was present. There was no hepatic disease to explain the hypoproteinemia and the reversal of the albumin-globulin ratio.

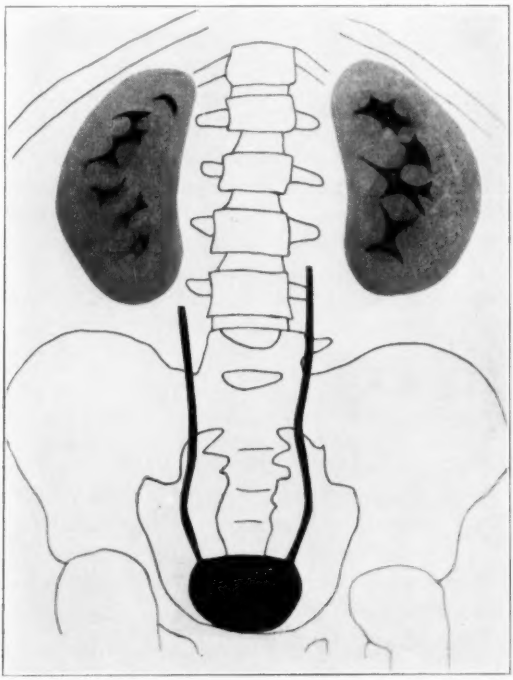

Fig. 10.—Schematic diagram of the pyelograms, showing pressure defects in the calices and pelves suggestive of polycystic disease.

Throughout the last fifteen months of the patient's illness all the cardinal signs of the nephrotic syndrome were repeatedly found with the exception of hypercholesteremia and the presence of doubly refractile bodies in the urine. However, the former was observed consistently during the last seven months. Doubly refractible bodies in the urine were observed on only two occasions, five and three months, respectively, before death.

19. Leiter, L.: Nephrosis, Medicine **10**:135, 1931.

If the chronic thrombosis of the renal veins was the sole background for the nephrotic syndrome, as seems likely, this case is unique. No other case of chronic thrombosis of the portal or renal veins with the nephrotic syndrome or of the nephrotic syndrome with chronic thrombosis of the renal veins has been found after careful search of the literature. The nearest approach is in cases of edema due to active glomerular nephritis, with acute thrombosis of the renal veins occurring terminally. Such cases differ from cases of the nephrotic syndrome because of the presence of normal levels of protein in the plasma [9b] and the rapid development of uremia.

SUMMARY

A case of chronic progressive occlusion of the inferior vena cava and the renal and portal veins, with the clinical picture of the nephrotic syndrome, in which death was due to pneumococcic peritonitis is reported. Pyelograms were suggestive of polycystic disease of the kidneys. The kidneys, however, showed only slight cloudy swelling of the tubules and edema of the interstitial tissue, with no abnormality of the glomeruli.

Drs. J. B. Manary and S. J. Thannhauser furnished data on the patient's condition during hospitalization elsewhere.

TENSE PNEUMOTHORAX

TREATMENT OF CHRONIC AND RECURRENT FORMS BY INDUCTION OF CHEMICAL PLEURITIS

HERMAN HENNELL, M.D.
AND
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Tense pneumothorax results when the communication between the lung and the pleura acts as a one way valve. Air can enter the pleural cavity during inspiration, but its escape is prevented during expiration, so that the pneumothorax tends to increase in size and tension. As the resulting dyspnea increases, the patient's inspiratory efforts become more vigorous, more air is pumped into the pleural cavity, and the condition is made more acute. This form of pneumothorax is not common, but it is important because of the distressing symptoms it may produce. Although it usually occurs as a complication of active pulmonary disease, there are instances in which there is little or no clinical evidence of a pathologic process in the lung and in which the etiology is not clear: cases of so-called idiopathic tense pneumothorax.

The majority of patients with valvular, or tense, pneumothorax get well under conservative management. After a while, so much air is aspirated into the pleural cavity that the intrapleural pressure is raised sufficiently to keep the valvelike tear in the lung closed during both phases of respiration. If the patient can then be kept quiet enough to avoid unusual respiratory effort, the opening in the lung will tend to heal. Air acts as an irritant and produces enough inflammatory reaction about the injured part of the lung to result in sealing of the defect. Once this occurs, the pneumothorax will be absorbed and the lung will reexpand.

There is, however, a certain group of cases in which this condition may persist for months or even years. The patients remain chronic invalids because of the respiratory and cardiac embarrassment which they may suffer on little exertion.

Once a chronic state has become established, a cure will not occur unless a more vigorous inflammatory pleural reaction supervenes and brings about the sealing of the chronic, partially epithelized pleuropul-

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monary communication. In this connection, it has been noted that the patients who for one reason or another contract active pleuritis with effusion recover soon afterward. This observation suggested the idea of attempting the induction of chemical pleuritis in cases of chronic and recurrent tense pneumothorax which showed no tendency to spontaneous recovery.

This idea first occurred to Spengler [1] in 1901. In 1906 he [2] suggested the use of a 0.5 per cent solution of silver nitrate for the production of the chemical pleuritis. In 1919 he [3] advised the use of a 30 per cent solution of dextrose for the same purpose. It was not until 1923 [4] that he reported his first clinical case. He used 30 cc. of a 30 per cent solution of dextrose in repeated doses and obtained a cure within four months. In his report he suggested that it would be desirable to use either larger amounts of the 30 per cent solution of dextrose (up to 100 cc.) or smaller quantities of a 50 per cent solution.

Kulcke [5] reported a case of chronic pneumothorax of three months' duration in a 9 year old child. A satisfactory result was obtained in six weeks after three injections of a 30 per cent solution of dextrose given ten days apart (20 cc., 35 cc. and 50 cc., respectively). Fogelberg and Wallgren [6] reported 2 clinical cures with the use of a 30 per cent solution of dextrose.

Brunner,[7] Kenner,[8] Schott [9] and Morlock [10] had no success with a 30 per cent solution of dextrose. Schott [11] obtained 2 clinical cures by using a 50 per cent solution of dextrose supplemented by temporary underwater drainage of the pneumothorax. Kenner [8] succeeded with 20 cc. of a 0.5 per cent solution of silver nitrate after failing with a 30 per cent solution of dextrose.

Single cases in which treatment was successful were reported by Morlock,[10] who used 5 cc. of a 1 per cent solution of silver nitrate; by Schott,[9] who used 0.5 cc. of oil of turpentine; by Watson and Rob-

1. Spengler, L.: Ztschr. f. Tuberk. **2**:27, 1901.
2. Spengler, L.: Beitr. z. klin. Chir. **49**:80, 1906.
3. Spengler, L., in Brauer, L.; Schröder, G., and Blumenfeld, F.: Handbuch der Tuberkulose, Leipzig, J. A. Barth, 1919, vol. 3, p. 232.
4. Spengler, L.: Schweiz. med. Wchnschr. **4**:310, 1923.
5. Kulcke, E.: München. med. Wchnschr. **67**:1175, 1920.
6. Fogelberg, H., and Wallgren, I.: Finska läk.-sällsk. handl. **66**:38, 1924.
7. Brunner: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:124, 1924.
8. Kenner, A.: Beitr. z. Klin. d. Tuberk. **80**:169, 1932.
9. Schott, E.: München. med. Wchnschr. **81**:716, 1934.
10. Morlock, H. V.: Proc. Roy. Soc. Med. **26**:525, 1933.
11. Schott, E.: München. med. Wchnschr. **82**:1751, 1935.

ertson,[12] who used venous blood, and by Apostolidés and Hadjissarantos,[13] who used guaiacol and iodoform. The use of a solution of silver nitrate and of oil of turpentine was followed by violent pleural reactions but led to ultimate cure.

Our review of the world literature disclosed the reports of no more than 12 cases of spontaneous pneumothorax treated by the induction of chemical pleuritis. The largest single series, comprising 3 cases, was reported by Schott.[14]

In the following report we shall describe the methods employed and the results obtained for 5 of 6 patients treated by us. The sixth left the hospital against advice before the treatment could be carried to completion. We shall also discuss the problems in pulmonary mechanics presented by these patients, especially their bearing on treatment. Obviously this series is too small to justify sweeping conclusions. We are of the opinion, however, that the value of the method has been demonstrated by the satisfactory results obtained in the 5 cases, namely, healing of the fistula and reexpansion of the lung.

REPORT OF CASES

CASE 1 (service of Dr. B. S. Oppenheimer).—J. F., a 46 year old Italian barber, entered the Mount Sinai Hospital on Aug. 13, 1934, complaining of severe shortness of breath of two and a half months' duration.

He was well until one year before admission to the hospital, when he experienced a sudden sharp pain in the right side of the chest. This was followed by weakness, which lasted for several hours. Ten weeks before admission he had a similar attack while lifting a heavy object. The pain was agonizing. It radiated from the right axilla to the epigastrium and lasted one hour. Although the patient felt extremely weak, he continued to be up and about for two days, until he was forced to bed by increasing shortness of breath. He remained bedridden until he was hospitalized. At no time did he complain of cough, expectoration or fever.

On physical examination, he appeared well nourished, dyspneic and somewhat cyanotic. The dyspnea became more marked at the least effort. The trachea deviated to the left. The right side of the chest was hyperresonant; breath sounds were diminished, and fremitus was absent over the right lung. The heart was displaced to the left, and the apex was felt in the midaxillary line.

Roentgen examination of the chest (fig. 1 *A*) revealed pneumothorax on the right, with almost complete collapse of the lung. The heart and the mediastinal structures were displaced to the left. There was no evidence of parenchymal pulmonary disease.

Management.—The clinical features of the case were those of tense pneumothorax, which had apparently existed for over ten weeks. Manometric readings

12. Watson, E. E., and Robertson, C.: Recurrent Spontaneous Pneumothorax: Report of Three Cases, Arch. Surg. **16**:431 (Jan., pt. 2) 1928.

13. Apostolidés, C., and Hadjissarantos, D.: Paris méd. **1**:338, 1930.

14. Footnotes 9 and 11.

of the intrapleural pressure on the right were made two days after admission and were found to be + 9 and + 12 cm. of water on quiet inspiration and expiration, respectively. In order that the patient might obtain relief from his acute dyspnea, 1,300 cc. of air was aspirated. This reduced the intrapleural pressure to — 5 cm. and — 1 cm. of water on quiet respiration. The relief afforded the patient was prompt but short lived. When manometric readings were taken one day later, they were + 9 and + 11 cm. of water on quiet inspiration and expiration, respectively. Obviously the tense pneumothorax had been promptly reestablished through the persisting valvelike defect in the lung and the visceral pleura.

We realized that spontaneous closure of the defect was not likely to occur, and we decided to attempt a cure by the induction of chemical pleuritis. We chose iodized poppyseed oil as the substance to be used for the following reasons: 1. We were familiar with its innocuousness for lung tissue from our bronchographic work. 2. We were anxious to demonstrate that the pleuropulmonary communication was truly a one-way valve, so that the iodized oil would not be able to leave the pleural cavity and would not enter the parenchyma of the lung.

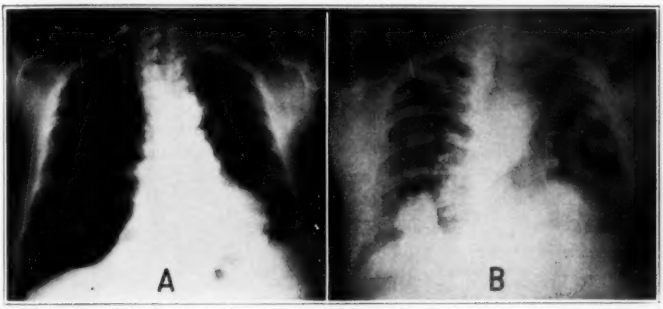

Fig. 1 (case 1).—*A*, roentgenogram showing a large pneumothorax on the right, with almost complete collapse of the lung. Note the marked displacement of the mediastinal structures to the left. *B*, roentgenogram showing complete reexpansion of the right lung. Note the circumscribed opaque patch representing the iodized oil on the pleural surface.

One week after the patient's admission 10 cc. of warmed iodized oil was injected into the right pleural cavity through an 18 gage needle attached to a Luer syringe. The skin and the wall of the chest were anesthetized in the usual manner by a 1 per cent solution of procaine hydrochloride. The patient received ⅙ grain (0.01 Gm.) of morphine sulfate subcutaneously about fifteen minutes before the procedure was started. In order that the iodized oil might spread over as much of the pleural surface as possible, the patient was instructed to change his position frequently during a short period following the injection of the oil. He experienced relatively little discomfort immediately after the injection. However, within about one hour he complained of a sense of tightness in the right side of the chest. Three hours later his temperature rose to 102.2 F., and there was considerable pain in the right side of the chest. A blood count made at this time showed 10,600 white cells per cubic millimeter. However, within a few hours the discomfort in the chest decreased, and the next day the temperature dropped to normal. The patient was kept comfortable with the aid of sedatives. He was

instructed to remain on his right side as continuously as possible and to refrain from coughing, from talking loudly and from other effort which might increase the respiratory excursion.

The object of these precautions was to keep the pleuropulmonary communication closed as continuously as possible and thus allow the inflammatory reaction to seal it. With the patient lying on the affected side the intrapleural pressure was raised to higher levels because of the effect of gravity on the mediastinal structures and because of the mechanical disadvantage of the respiratory muscles of the affected hemithorax. This was verified by manometric determination of the intrapleural pressure with the patient in various positions of recumbency. The importance of avoiding sudden increase in the inspiratory effort will also be readily appreciated. In order to keep the valvelike communication continuously closed, the intrapleural pressure must remain above the atmospheric pressure during the inspiratory phase of respiration. This is not difficult to accomplish during quiet respiration. However, a strong inspiratory effort may transform moderately positive pressure during quiet inspiration into negative pressure of a considerable degree and may thus result in the reopening of the valvelike defect in the lung which was tending to be sealed over by the inflammatory pleural reaction.

On the day following the injection of the iodized oil, a succussion splash could be elicited, and roentgen examination showed a small effusion. During the ensuing week the dyspnea progressively decreased. On the eighth day after the induction of the chemical pleuritis the manometric readings of the intrapleural pressure were —6 cm. and +1 cm. of water on quiet respiration. This indicated the probable closure of the valvelike defect in the visceral pleura and the lung. In order that this probability might be confirmed, 950 cc. of air was aspirated. As expected, the manometric readings became more definitely negative (—8 and —2 cm.). This last maneuver proved to be ill advised. It resulted in the reopening of the recently sealed defect, as was shown the next day, when the manometric readings on quiet respiration were +3 and +8 cm.

We therefore introduced another 10 cc. of iodized oil into the pleural cavity in a second attempt to produce active chemical pleuritis. It is of interest that the local and the constitutional response to this were identical with those detailed in the description of the first injection of iodized oil. Thirteen days later the manometric readings on quiet respiration were —4 cm. and 0 cm. Roentgen examination made at this time showed considerable reexpansion of the right lung.

In order that the danger of reestablishing the pleuropulmonary communication might be avoided the patient was kept at rest in bed, remaining as quiet as possible. One week later the right lung showed 50 per cent reexpansion. The patient was allowed to leave the hospital and to continue his convalescence at home.

From this time reexpansion of the lung progressed uneventfully. Five weeks after the patient's discharge from the hospital (two months after the successful induction of chemical pleuritis) there was only a small residual hydropneumothorax. One month later the lung was completely reexpanded, the fluid was entirely absorbed, and the iodized oil appeared as a circumscribed opaque patch on the pleural surface. The patient remained entirely well. When seen three and a half years later he was in good health. He has had no recurrence of spontaneous pneumothorax (fig. 1 *B*). It is probable that the pleuritis has caused sufficient agglutination of the pleural surfaces to prevent recurrence of the pneumothorax which is so common in cases of the idiopathic type.

CASE 2 (service of Dr. R. Colp).—P. D., a 5 year old boy, was first admitted to the Mount Sinai Hospital on Jan. 5, 1935, with postpneumonic pyopneumothorax on the left and purulent pericarditis. He was treated first by a stab

thoracotomy and then by rib resection and pericardiotomy. His clinical course was stormy and included the development of an empyema on the right, which also had to be drained. After the acute inflammatory process had been controlled, two serious complications became evident: (1) cardiac failure, apparently resulting from the pericardial process, and (2) pyopneumothorax on the left with a persistent bronchopleural communication. The cardiac failure was controlled by mercurial diuretics and digitalis. The pyopneumothorax was treated by drainage through a "flapper" tube. This tube allowed the drainage of pus and air during expiration but prevented the entrance of air during inspiration. After four months of hospitalization cardiac compensation was restored, drainage was discontinued, and the wound in the chest was allowed to heal. The child's condition improved sufficiently to permit his discharge from the hospital. However, in spite of the healing of the wound, the pneumothorax failed to absorb.

Two and a half months later the child was readmitted because of the persistence of the pneumothorax. After the healing of the wound in the chest the pneumothorax developed the characteristics of the tense form, with marked displacement of mediastinal structures toward the uninvolved side.

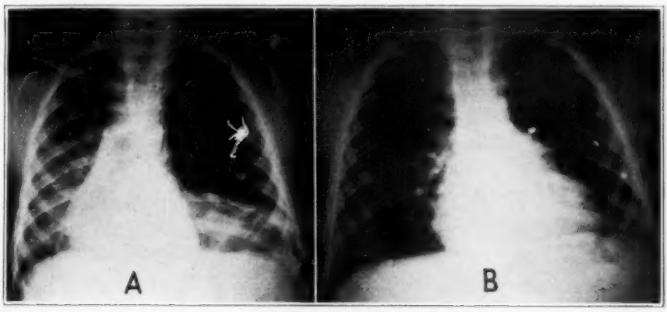

Fig. 2 (case 2).—*A*, roentgenogram showing a large pneumothorax on the left. Note the marked herniation of the mediastinal structures into the right hemithorax. *B*, roentgenogram showing the complete reexpansion of the left lung. Note the small patches of iodized oil scattered over the pleural surface.

Physical examination at this time showed bulging of the left hemithorax, with greatly diminished respiratory excursions. There was tympany over the anterior aspect of the left side of the chest. The maximum cardiac impulse was felt and heard in the fourth intercostal space to the right of the sternum. Roentgen examination (fig. 2 *A*) disclosed marked herniation of the mediastinal structures into the right hemithorax.

Management.—It was obvious that chronic tense pneumothorax was present in this case. Measurement of the intrapleural pressure shortly after the child's admission showed manometric readings of + 3 and + 12 cm. of water on quiet inspiration and expiration, respectively. These findings indicated the existence of a one way valve communicating between the pleural cavity and the lung. In order that this probability might be confirmed, 550 cc. of air was aspirated from the left pleural cavity. A temporary reduction of the pleural pressure was obtained. However, after a few minutes of deep respiration the pleural pressure

was again + 3 and + 8 cm. of water on quiet inspiration and expiration, respectively. This maneuver proved conclusively that a one way communication existed between the lung and the pleural cavity.

Because of the long duration of the process it was felt that spontaneous recovery was not likely to occur. It seemed doubtful whether the induction of chemical pleuritis would prove helpful in sealing over the valvelike defect in the lung and the visceral pleura. This pleura had been the seat of severe inflammatory reaction only a few months previously. It was therefore thought that it was not likely to respond to simple chemical irritation with inflammatory reaction sufficiently active to obliterate the chronic defect. However, since no other simple remedy was available, we decided to try this procedure. Accordingly, 10 cc. of iodized oil was injected into the left pleural space with the technic previously described. The child did not complain of pain in the chest after this procedure. Twenty-four hours later the temperature rose from 99 to 100.4 F. Another rise, this time to 101 F., occurred six days later. On the sixteenth day the intrapleural pressure was 0 cm. and + 6 cm. of water on quiet inspiration and expiration, respectively. Roentgen examination two days later showed considerable absorption of the pneumothorax and partial return of the mediastinal structures to the central position. Subsequently absorption of the pneumothorax and reexpansion of the left lung continued without interruption. Seven weeks after the induction of the pleuritis, roentgen examination showed that the pneumothorax occupied about 33 per cent of the left pleural cavity and that the mediastinal structures had returned to the normal position. Within six months the lung had entirely reexpanded. Two and a half years later (the time of writing) the child was perfectly well; the left lung was fully reexpanded and showed no abnormality. The iodized oil could still be seen scattered in small patches over the pleura (fig. 2*B*).

It is of interest that the iodized oil was able to produce a chemical pleuritis which effectively healed the chronic pleuropulmonary communication despite the fact that the pleura had previously been the seat of a severe inflammatory process. Apparently the initial acute pleuritis was not able to produce healing of the by-pass fistula which existed at the time, and the pleural inflammation had completely subsided before a check valve mechanism developed and the conditions became favorable for the permanent closure of the bronchial fistula. The acute inflammatory reaction evoked by the introduction of iodized oil into the pleural cavity produced freshening of the partially epithelized fistula and thus favored its healing after it had been kept closed for a while by the high intrapleural pressure which was present (as a result of the check valve mechanism which had developed in the meantime).

Case 3 (service of Dr. B. S. Oppenheimer).—A. S., a 15½ year old school girl, entered the Mount Sinai Hospital on Sept. 30, 1937, complaining of shortness of breath and of a nonproductive cough.

Two years before admission she began to have shortness of breath on little exertion. This was not progressive. She did not remember having experienced pain in the chest at any time. Six months before admission a nonproductive cough developed. At that time a school physician advised roentgen examination of the chest, but because of the mildness of the symptoms this advice was not

heeded. During the past two months her cough had produced a small amount of whitish sputum. There was also some loss of weight. One week before the patient's admission roentgen examination of the chest was made and hospitalization was advised.

Physical examination on admission revealed a well nourished young girl who was in no respiratory distress when at rest. The right hemithorax moved little on respiration. The trachea deviated slightly to the left. The right side of the chest was hyperresonant. The breath sounds over the right lung were diminished in intensity and had an amphoric quality. The heart did not appear to be displaced.

Roentgen examination (fig. 3 *A*) revealed a large pneumothorax on the right with complete collapse of the lung. The heart and the mediastinal structures were slightly displaced to the left.

The sputum contained no tubercle bacilli. The tuberculin reaction was negative.

Management.—This was obviously a case of chronic pneumothorax. The probable duration of the condition could only be surmised. It appeared certain

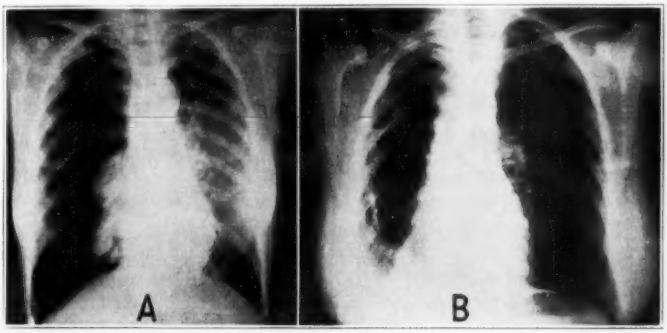

Fig. 3 (case 3).—*A*, roentgenogram showing complete collapse of the right lung by a large pneumothorax. The mediastinal structures are displaced slightly to the left. *B*, roentgenogram showing almost complete absorption of the pneumothorax. The lung has not as yet fully reexpanded. The mediastinal structures are displaced considerably to the right, and the right leaf of the diaphragm is moderately elevated.

that the pneumothorax was present six months before the girl's admission, at the time the school physician advised roentgen study of the chest. Furthermore, it was most probable that the dyspnea, which was first noted two years before admission but was not progressive, was due to the pneumothorax present at that time.

The chronicity of the process could be inferred from the history. While the physical and roentgen findings did not suggest the existence of a tense pneumothorax, in view of the relatively insignificant displacement of the mediastinal structures, manometric readings showed the intrapleural pressure to be $+2$ and $+3$ cm. of water on quiet inspiration and expiration, respectively. The lack of displacement of the mediastinal structures indicated that they did not possess the normal degree of flexibility. An antecedent inflammatory process involving the

mediastinal pleura was therefore suspected. Whether the process was related to underlying disease in the lung or was the result of the mechanical irritation of chronic pneumothorax could not be definitely determined.

Management.—The finding of a positive intrapleural pressure on quiet respiration indicated that the pneumothorax was periodically renewed through a persistent one way bronchopleural communication. Because of the long duration of the pneumothorax a spontaneous cure was not likely to occur. We therefore decided to induce chemical pleuritis in an attempt to produce healing of the defect in the lung. Our experience in the first 2 cases, in which we had used iodized oil as the irritant, had been satisfactory enough to warrant repetition of this treatment. However, the iodized oil had shown one objectionable feature: It had failed to become absorbed. We therefore decided to use a 50 per cent aqueous solution of dextrose. Accordingly, 50 cc. of such a solution was introduced into the space occupied by the pneumothorax. The patient experienced little discomfort either at the time of injection or at any time thereafter. There was no rise in temperature or change in the leukocytic picture. One week later the manometric readings were —5 cm. and 0 cm. of water during quiet inspiration and expiration, respectively. At the same time roentgen examination showed the pneumothorax to be smaller and the right lung partially reexpanded. There was also a small pleural effusion. This was evidence that active pleuritis had been produced.

One month later it was noted that the lung, instead of reexpanding further, had again become completely collapsed. Apparently after the expansion of the lung had reached a certain point, the defect in the lung and the visceral pleura had reopened, with consequent recurrence of the original tense pneumothorax.

We therefore attempted to produce more acute pleuritis by injecting 60 cc. of a 67 per cent solution of dextrose. This procedure was repeated two weeks later. The result was similar to that of the original injection: After temporary closure, the pleuropulmonary communication reopened when the reexpansion of the lung had reached a certain point.

We then decided to use iodized oil, in the hope that it would prove a more potent irritant. Twelve cubic centimeters of oil was injected into the right pleural cavity. The patient experienced considerable discomfort in the chest shortly after the injection. The next day her temperature rose to 101 F. The pain and fever subsided within forty-eight hours.

Two days later there was moderate pleural effusion, evidenced by a succussion splash. Manometric readings showed the intrapleural pressure to be —8 cm. and 0 cm. on quiet inspiration and expiration, respectively. Roentgen examination at this time showed that the pneumothorax had decreased in size and that the right lung showed considerable reexpansion. Two months after the injection of the iodized oil there was marked decrease in the size of the pneumothorax; the lung reexpanded proportionately, and the manometric readings were —12 and —4 cm. of water on quiet inspiration and expiration, respectively.

The regimen of sedatives and rest in bed with the patient lying on the involved side was continued throughout this period. Only after repeated observation had convinced us that the pleuropulmonary communication was safely closed was the patient allowed moderate activity. Roentgen examination six months after the injection of iodized oil (fig. 3*B*) showed that the pneumothorax had almost completely disappeared, the lung had reexpanded in proportion and the effusion had been absorbed. However, it was noted that the mediastinal structures were considerably displaced to the right and that the right leaf of the diaphragm was elevated.

Apparently the visceral pleura had reacted to prolonged irritations with formation of so much fibrous tissue that complete reexpansion of the lung was prevented. Failure of the lung to reexpand completely had in turn caused the displacement of the mediastinum and of the right leaf of the diaphragm.

Although the lung had not returned to a state of full inflation, we feel that the therapeutic result achieved is most gratifying.

CASE 4 (service of Dr. B. S. Oppenheimer).—H. G., a 39 year old shoe salesman, entered the Mount Sinai Hospital on May 25, 1937, complaining of shortness of breath which had lasted nine months. Arterial hypertension had been discovered eight years previously, but it had caused relatively little disability. Nine months before admission to the hospital, while taking a shower bath, the man suddenly felt a severe stabbing pain in the right side of the chest. A physician who examined him by fluoroscope told him that he had pneumothorax on the right. The patient continued his usual activities, though he was disturbed by dyspnea on mild exertion. He was observed at regular intervals by his physician, and because of the persistence of the pneumothorax at the end of nine months he was hospitalized.

On admission the patient appeared well developed. He showed moderate dyspnea on little exertion. Physical and roentgen examination of the chest revealed a pneumothorax on the right with complete collapse of the lung. The heart was enlarged but was only slightly displaced to the left. The blood pressure was 260 mm. of mercury systolic and 140 mm. diastolic. There were no signs or symptoms of cardiac insufficiency.

Management.—The diagnosis of chronic tense pneumothorax was made on the basis of the history and of the physical and the roentgen findings. This diagnosis was definitely established when the manometric readings of the intrapleural pressure were found to be + 4 and + 10 cm. of water on quiet inspiration and expiration, respectively. The fact that the mediastinum was only slightly shifted to the left was due to the inflexibility of this structure, because of which the pneumothorax, although it was under considerable tension, produced little embarrassment to the patient. Although the tense pneumothorax appeared to cause little discomfort, it was felt that it would be a great gain if the function of the right lung could be restored.

We therefore decided to treat the patient by the induction of chemical pleuritis. Accordingly, 50 cc. of a 50 per cent solution of dextrose was introduced into the right pleural cavity. As no evidence of pleuritis and no change in the size of the pneumothorax were noted after one week, 25 cc. of a 67 per cent solution of dextrose was injected. There was no febrile reaction, but the patient complained of pain in the right side of the chest. Physical and roentgen examination gave evidence of moderate pleural effusion. Within one week the upper and the middle lobe of the right lung reexpanded to 40 per cent of their normal volume, and manometric readings showed — 5 and + 4 cm. of water on quiet respiration, indicating closure of the pleuropulmonary communication. Several days later the right lung was found to have reexpanded 75 per cent. At this time the patient was allowed to be out of bed. This liberty was apparently premature. It resulted in the reopening of the pleuropulmonary communication, as shown by recurrence of the collapse of the lung and rise of the intrapleural pressure to + 1 cm. and + 6 cm. of water on quiet respiration. This experience emphasized that prolonged

rest in bed during the course of the active pleuritis is necessary to insure firm closure of the pleuropulmonary communication. The treatment was repeated, with 45 cc. of a 67 per cent solution of dextrose. The patient was kept at strict rest in bed, which was supplemented by sedatives, for three weeks. During this period there was progressive reexpansion of the lung. Within one month it was almost completely reexpanded. The patient was then discharged from the hospital and allowed moderate activity. Six months later he was well, and roentgen examination of his chest showed no evidence of pneumothorax. The right lung showed no abnormality.

Case 5 (service of Dr. B. S. Oppenheimer).—M. B., a 47 year old compositor and pressman, was admitted to the Mount Sinai Hospital on Jan. 16, 1938, because of recurring attacks of severe dyspnea during the previous six months.

He had no previous history of significant pulmonary disease, and he had been in good health for many years prior to the onset of the present illness.

Early in July 1937 he experienced sudden severe pain in the left side of the chest after climbing a flight of stairs. The acute pain lasted only a few minutes, but it left him with considerable dyspnea on little exertion. A mild nonproductive cough developed. As these symptoms rapidly became worse, the patient consulted a physician. He was advised to rest in bed and was treated with digitalis. These measures afforded him no relief. Dyspnea and orthopnea became increasingly more distressing, and the patient had to be treated with inhalations of oxygen. At this time roentgen examination of the chest showed evidence of a large pneumothorax on the left and of bilateral tuberculosis of the upper lobes. The patient was therefore sent to an institution for the tuberculous.

At the time of his transfer to the sanatorium the patient's respiratory distress was so marked that oxygen therapy had to be administered during the journey of a hundred miles (160 kilometers). On arrival at the sanatorium aspirations of air were employed several times, at intervals twelve to thirty-six hours apart, to afford the patient relief from severe dyspnea.

The acute symptoms subsided after a few days' stay in the sanatorium. Because of a suspicion of active tuberculous disease it was decided to maintain the pneumothorax at low tension by small refills administered every three or four days. However, when after three months of observation the various studies failed to disclose evidence of active tuberculosis, the left lung was allowed to reexpand. The patient was permitted increasing amounts of activity during the succeeding two months and was discharged from the sanatorium apparently well at the end of a five months' stay.

Three weeks later he experienced a sudden recurrence of suffocative dyspnea and was admitted to the Mount Sinai Hospital with the diagnosis of recurrent pneumothorax on the left.

On admission the patient showed marked dyspnea and orthopnea, which were greatly increased on the least effort or excitement. The physical signs in the lungs were those of tense pneumothorax on the left with considerable displacement of the mediastinal structures to the right. The heart rate was 120 per minute, and there was definite evidence of cardiac embarrassment. The blood pressure was 150 mm. of mercury systolic and 96 mm. diastolic. The venous pressure was 10.5 cm., rising to 11.5 cm. on pressure on the right upper quadrant. The saccharin circulation time was eighteen seconds.

Roentgen examination (fig. 4 *A*) showed a large pneumothorax on the left which collapsed the left lung and displaced the mediastinum considerably to the

right. The upper lobe of the right lung was shrunken as a result of a fibrotic tuberculous process, and the lower lobes showed fibrotic strands, marked emphysema and emphysematous blebs.

Management.—The diagnosis of recurrent tense pneumothorax was obvious. The manometric readings in the left pleural cavity during quiet respiration were + 6 and + 20 cm. of water on inspiration and expiration, respectively. The patient appeared nervous on admission and was much alarmed by his symptoms. Having obtained relief from aspiration of air on previous occasions, he was pleading for this treatment. The futility of the procedure was explained to him. He was advised to remain as quiet as possible and to refrain from exaggerated respiratory effort in order to avoid the marked rise in intrapleural pressure which was responsible for his distress. However, it was not possible to keep him sufficiently quiet the first few days, and aspiration of about 300 cc. of air had to be performed several times to give him relief from the recurring acute symptoms.

Since the patient had spontaneously recovered from pneumothorax five months previously, spontaneous cure might have been anticipated on this occasion as well.

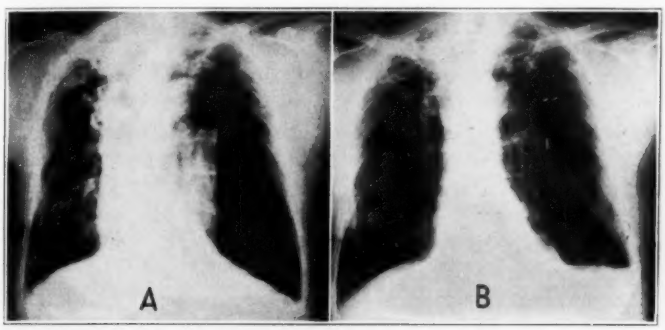

Fig. 4 (case 5).—*A*, roentgenogram showing a large pneumothorax on the left, with collapse of the left lung and considerable displacement of the mediastinum to the right. Note the fibroid tuberculous lesion in the upper lobe of the right lung and the emphysematous blebs in the lower lobes. *B*, roentgenogram showing the left lung completely reexpanded. Note the extensive emphysematous changes with formation of blebs in the reexpanded left lung.

However, we decided to treat him by the induction of chemical pleuritis for the following reasons: 1. Spontaneous cure might not take place again. 2. Closure of the pleuropulmonary communication might be achieved more quickly by induced pleuritis. 3. The induced pleuritis might result in agglutination of the pleural surfaces and thus prevent recurrence of tense pneumothorax, which had been so distressing.

The technic employed in the preceding cases was used. First 50 cc. of a 50 per cent solution of dextrose was used, but without success. However, effective pleuritis was induced by injection of 65 cc. of a 67 per cent solution of dextrose into the cavity of the pneumothorax. Nine days later the pleural pressure fell to — 3 and + 7 cm. of water on quiet respiration, and fluoroscopic study showed considerable resorption of the pneumothorax. After four weeks the left lung was almost completely reexpanded. From that time the patient's progress continued without interruption, and he was soon able to resume normal activity.

When last seen, in June 1938, he was well. The left lung had remained fully reexpanded. Roentgen examination showed the left lung, as well as the right, to be the seat of a fibrotic tuberculous process in the upper lobe and of extensive emphysematous changes with formation of blebs in the lower lobe (fig. 4 *B*).

It is probable that the rupture of one of these emphysematous blebs was responsible for the recurrent valvular pneumothorax in the past, and it is hoped that the induced pleuritis may prevent such recurrences in the future.

COMMENT

The cure of tense pneumothorax will take place as soon as the pleuropulmonary communication has permanently healed. Healing will depend on two factors: (1) the maintenance of a positive intrapleural pressure to keep the opening closed during both phases of respiration and (2) the production of a pleural reaction sufficient to seal the opening permanently. These are the objectives in the management of chronic tense pneumothorax. The 5 cases show how these objectives have been obtained under varying conditions. They also demonstrate how much the treatment depends on correct understanding of the underlying mechanism. These aspects of the subject merit some general comment.

Mechanism.—The existence of chronic pneumothorax presupposes the presence of a persistent pleuropulmonary communication. This communication may be either a two way or a one way valve. With a pleuropulmonary communication of the two way type, air can enter the pleural cavity during inspiration and leave it during expiration. This will occur if the defect in the lung is relatively large and stiff walled. Under such circumstances the pleural pressure is a few centimeters of water below 0 during inspiration and an equal number of centimeters above 0 during expiration. Whether the mediastinum is displaced under these conditions depends on its relative flexibility. With a flexible mediastinum marked displacement may occur even with low pleural pressure, and the condition may simulate true tense pneumothorax in every detail. Whether our present method of treatment will prove adequate for a condition of this type is problematic and can be determined by trial only; a patient with such an involvement has recently come under our care, and the result of treatment will be reported at a later date.

When the pleuropulmonary communication is of the one way, or check valve, type, air can enter the pleural cavity during inspiration if the intrapleural pressure created is below the atmospheric pressure, but cannot leave it during expiration when the pleural pressure is above the atmospheric pressure. The size and tension which the pneumothorax can attain under such circumstances will depend primarily on the forcefulness of the inspiratory effort and only to a lesser extent on the flexibility of the mediastinum. The opening and closing of the one way valve is automatically determined by conditions of pressure in the pneu-

mothorax cavity. When the pressure is high enough, the valve remains closed during both phases of respiration. The pneumothorax cavity is then closed, and air is absorbed from it according to the principles governing absorption of air in such a case. As air is absorbed and the pressure in the pleural cavity falls progressively, a point is soon reached where it becomes lower than the atmospheric pressure during the inspiratory phase of respiration. More air can enter the pleural cavity, thus renewing and perpetuating the tense pneumothorax. Coughing, laughing and excitement, with attendant forceful inspiratory effort, are important factors in the recreation and maintenance of the tense pneumothorax. It is because of these considerations that one of the objectives in the management of this condition is to maintain a positive intrapleural pressure to keep the opening closed during both phases of respiration. This will be discussed later, when accessory measures are considered.

The severity of the symptoms produced by a tense pneumothorax is determined in addition by the integrity of the functioning lung, the flexibility of the mediastinum and the condition of the heart. This was well illustrated in the fourth and the fifth case. In case 5 there was a marked degree of respiratory and cardiac embarrassment. In case 4 these symptoms were mild, despite the facts that the size and tension of the pneumothorax were greater in this case and that there was, in addition, associated marked arterial hypertension. This apparent discrepancy may be explained by the following circumstances: In case 5 the function of the sound lung was greatly reduced by the disseminated fibrosis and emphysema as well as by the encroachment of the flexible mediastinum. In addition, there was in this case latent myocardial insufficiency (as a result of chronic pulmonary disease and of independent disease of the coronary arteries). By contrast, in case 4 the functioning lung was in a healthy state, the mediastinum was relatively inflexible, and the heart was apparently in good condition.

Management.—In describing the management of these cases we emphasized the importance of the accessory measures which we employed in addition to the induction of chemical pleuritis. These included rest in bed with the patient lying on the affected side, judicious use of sedatives and avoidance of undue inspiratory effort. The object of the accessory procedures was to keep the pleuropulmonary communication closed during both phases of respiration. The rationale was discussed in detail in connection with case 1.

The question of aspiration of air also received due consideration. The futility and harmfulness of this procedure have been repeatedly demonstrated in connection with the management of the pneumothorax in 4 of the 5 cases. There should be no occasion to aspirate even small amounts of air for the relief of acute symptoms if the correct general regimen is followed.

In general, it must be stressed that scrupulous attention to the details of the described regimen is essential if one is to secure the desired results, namely, the permanent closure of the fistula and the reexpansion of the lung.

As to the choice of the agent for inducing chemical pleuritis, we are inclined to limit ourselves for the present to a 67 per cent aqueous solution of dextrose in amounts varying from 50 to 60 cc. and to iodized oil in amounts of 10 to 12 cc. While a 50 per cent aqueous solution of dextrose may be inadequate, a 67 per cent solution (saturated) is more likely to produce effective pleuritis, and it is just as safe as the less concentrated solution. It appears to us that the amount of solution used is less important than its concentration. We have used as little as 25 cc. and as much as 60 cc. with equally satisfactory results. The size of the pneumothorax cavity has been a rough guide to the amount of dextrose solution required, and 50 cc. was the average quantity used.

When a saturated solution of dextrose failed to produce a cure in 1 of our cases, the use of iodized oil proved effective. The latter substance produced a much more acute reaction, as shown by thoracic discomfort, by a greater amount of effusion (which also appeared more promptly) and by constitutional symptoms.

It must be borne in mind that it was frequently necessary to repeat the injection if one attempt had failed; this was true of both a solution of dextrose and iodized oil. In the sixth case, which we did not report, both a solution of dextrose and iodized oil failed to produce a cure. However, had this patient not left the hospital against advice, further attempts would have been made to induce effective pleuritis, either by using iodized oil again or by employing a still more active irritant.

Whether we could have ultimately succeeded in that case cannot be stated with any degree of assurance. That our method will not succeed in all cases of chronic tense pneumothorax cannot be doubted. We are of the opinion, however, that the satisfactory results obtained in 5 of our 6 cases definitely established the value of the method.

SUMMARY

Tense pneumothorax results when a pleuropulmonary communication acts as a one way valve, allowing air to enter the pleural cavity during inspiration and preventing its escape during expiration.

Anything that will increase the inspiratory effort of the patient (dyspnea, cough, etc.) will allow more air to enter the pleural cavity, increasing the size and tension of the pneumothorax and thus aggravating the symptoms.

In most instances tense pneumothorax cures itself. When sufficient air enters the pleural cavity, the lung collapses, and the valvelike defect is closed. Healing of this defect will result if the collapse of the lung can be maintained by a moderately positive intrapleural pressure during inspiration as well as during expiration. Air in the pleural cavity acts as an irritant and usually produces sufficient inflammatory reaction to seal the defect. Once the pleuropulmonary communication is permanently closed, the pneumothorax will be absorbed, and the lung will reexpand.

Occasionally the tense pneumothorax persists in a chronic form for months or years, and the victim remains a chronic invalid because of the respiratory and cardiac embarrassment which he may suffer on little exertion.

By the induction of chemical pleuritis of greater or lesser severity it has been possible to produce healing of the chronic pleuropulmonary communication. A clinical cure occurred in 5 of 6 cases in which this method was tried. In the sixth case the patient left the hospital before the treatment could be completed.

Iodized oil and a concentrated solution of dextrose were used as the chemical irritants. The technic employed is described in detail in the case reports.

The following accessory measures are essential to keep the pleuropulmonary communication closed so that it may be permanently sealed by the induced chemical pleuritis: prolonged rest in bed, with the patient lying on the affected side; the judicious use of sedatives; the suppression of all acts attended by increased respiratory effort, and the avoidance of aspiration of air.

The mechanism underlying tense pneumothorax and its cure has been discussed in detail because of the important bearing it has on treatment.

SEDIMENTATION RATE AND NONFILAMENT-FILAMENT RATIO IN LOW GRADE CHRONIC ILLNESS

A STATISTICAL ANALYSIS OF 292 CASES

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Although many articles have appeared on the variations in the sedimentation rate and nuclear count, little has been written on these subjects in relation to low grade chronic diseases, except tuberculosis and chronic arthritis, which have been studied extensively, and ulcerative colitis, concerning which an article has recently been published.[1]

The sedimentation rate has been reported as normal in focal infections,[2] muscular rheumatism [3] and peptic ulcer without complications.[4] Sjögren [5] reported that its determination was "useful in latent infections of the eye."

In regard to nuclear counts, it has been stated that in "all important focal infections" [6] and "long-continued or low-grade infection" [7] there is a rise in the Schilling index and that there is "in chronic conditions a persistent high shift," [8] and there have been such conflicting statements

1. Garvin, R. O., and Bargen, J. A.: The Hematologic Picture of Chronic Ulcerative Colitis, Am. J. M. Sc. **193**:744 (June) 1937.

2. Merritt, W. A.: The Sedimentation Rate in General Practice, Minnesota Med. **20**:99 (Feb.) 1937. Biern, O. B.: Value of the Sedimentation Rate in Medicine, West Virginia M. J. **33**:289 (July) 1937.

3. Schulten, H.: The Determination of the Sedimentation Rate of the Red Blood Corpuscles and Its Importance in Internal Medicine, Med. Klin. **27**:125 (Jan. 23) 1931.

4. Schindler, J. A., and Gnagi, W. B., Jr.: The Sedimentation Rate in General Practice, Wisconsin M. J. **34**:531 (Aug.) 1935.

5. Sjögren, H.: Blood Picture and Sedimentation Reaction in Inflammatory Diseases of Eye, Hygiea **97**:262 (April 15) 1935.

6. Griffith, W. H.: The Schilling Hemogram in Acute Infections, Journal-Lancet **57**:239 (June) 1937.

7. Crocker, W. J., and Valentine, E. H.: Hemography in Diagnosis, Prognosis, and Treatment Based on Six Thousand Schilling Hemograms, J. Lab. & Clin. Med. **20**:172 (Nov.) 1934.

8. Gradwohl, R. B. H.: The Schilling Blood Methods, South. Med. & Surg. **94**:53 (Feb.) 1932.

as that of Rosenfeld,[9] that in chronic appendicitis the blood picture is normal, and that of Crocker and Valentine,[10] that in chronic fibrous appendicitis the total number of shift cells ranges from 10 to 35, with a Schilling index of ¼ to 1.[10]

The present study was undertaken to determine the extent of variation in sedimentation rate and nuclear count in patients with chronic low grade diseases.

CLINICAL DATA

Studies of the blood were made on 292 patients with chronic or frequently recurring symptoms, many of which were possibly secondary to low grade chronic infections. The patients studied, with few exceptions, were ambulant. While all age groups were included, the youngest patient studied being 2 years old and the oldest over 80, the majority of patients were young adults.

Of the 292 patients, most of whom had more than one disease, there were 146 with classic evidence of chronic sinusitis. Among the remainder, careful questioning and examination revealed the presence in 131 of such abnormalities as nasal congestion, postnasal discharge and inflammation of the nasopharynx, which Burbank [11] called evidence of chronic nasopharyngitis. If the criteria of such writers as Chase [12] are accepted, the latter group would also be classified as having chronic sinusitis. Of the total number of patients, 131 complained of frequent "colds."

Thirteen patients had chronic infections of the ear or mastoid, and 52 had chronic bronchitis, but only 10 showed evidence of chronic tonsillitis, and only 15, evidence of other oral infection. The low incidence of oral infection was probably due to the fact that the tonsils had previously been removed and the teeth had had excellent care in most cases.

There were 41 cases of colitis, 37 of other chronic or recurrent gastrointestinal conditions and 75 in which symptoms were referable to the biliary tract. Infections of the urinary tract occurred in 36 cases and prostatitis in 9. There were 14 cases of rheumatoid arthritis, 26 of other forms of arthritis, 7 of bursitis and 36 of "rheumatism," the

9. Rosenfeld, E. B.: The Clinical Significance of Schilling's Hemogram, Vrach. gaz. **31**:175, 1927.

10. Crocker, W. J., and Valentine, E. H.: Hemography in the Diagnosis of Appendicitis Based on Five Hundred Cases, J. Lab. & Clin. Med. **21**:883 (June) 1936.

11. Burbank, R.: Chronic Arthritis, J. A. M. A. **99**:1489 (Oct. 29) 1932.

12. Chase, W. D.: Etiology and Diagnosis of Sinusitis, Pennsylvania M. J. **39**:389 (March) 1936.

patients having fleeting pains in the joints, muscular pain, stiffness and similar symptoms, which have been called "prodromes to arthritis."[13]

Of the aforementioned conditions, in which infection is rather generally considered to play a part, at least one was present in each patient. In addition 4 patients had nephritis, 14 migraine, 18 duodenal ulcer, 3 urticaria, 16 asthma, 16 hay fever, 3 eczema, 2 vasomotor rhinitis, 4 diabetes, 1 Ménière's disease and 3 thyrotoxicosis.

Patients were grouped according to severity of illness as having mild or recurrent, moderately severe or severe symptoms. An additional group included patients the severity of whose symptoms was more or less acutely increased above the customary level. In assigning patients to a group opinions were based on the severity of the disease process, rather than on subjective symptoms, psychogenic factors being discounted as far as possible.

METHODS

Routine blood counts and determinations of sedimentation rate were made on all patients. Variations in the sedimentation rate and in the nuclear count were the most frequent changes noted and are reported here. Since most of the nuclear counts showed not only an increase in the percentage of nonfilamented cells but a decrease in the percentage of filamented cells, it was thought that the ratio between nonfilamented and filamented neutrophils gave a better representation of the neutrophilic change than the percentage of nonfilamented cells alone.

In making differential blood counts neutrophilic leukocytes were divided into nonfilamented and filamented types according to the criterion of Haden;[14] i. e., "neutrophils in which two or more lobes are united only by a filament of chromatin material are recorded as filamented cells, all others are classified as nonfilamented." The ratio of nonfilamented to filamented neutrophils (referred to as the "nonfilament-filament ratio") was expressed in percentages, $\left(\frac{\text{nonfilamented cells} \times 100}{\text{filamented cells}}\right)$.

The sedimentation rate was determined by the method of Westergren. About 2 cc. of venous blood was introduced into a small vial containing a pinch of lithium oxalate. After gentle agitation the blood was drawn up to the 200 mm. mark on a Westergren tube. At the end of one hour the height of the column of clear fluid was recorded in millimeters. Dry lithium oxalate was considered a satisfactory anticoagulant since in a control series of tests with dry potassium oxalate, which was not considered to increase the sedimentation rate above that obtained with heparin,[15] the results were parallel except that in the higher ranges, above 30 mm., the readings with lithium oxalate averaged 5 to 10 mm. lower than those

13. Hench, P. S.; Bauer, W.; Fletcher, A. A.; Ghrist, D.; Hall, F., and White, P.: The Present Status of the Problem of "Rheumatism," Ann. Int. Med. **8**:1517 (May) 1935.

14. Haden, R. L.: Qualitative Changes in Neutrophilic Leukocytes, Am. J. Clin. Path. **5**:354 (Sept.) 1935.

15. (*a*) Bannick, E. G.; Gregg, R. O., and Guernsey, C. M.: The Erythrocyte Sedimentation Rate, J. A. M. A. **109**:1257 (Oct. 16) 1937. (*b*) Wintrobe, M. M., and Landsberg, J. W.: Standardized Technic for Sedimentation Test, Am. J. M. Sc. **189**:102 (Jan.) 1935. (*c*) Greisheimer, E. M.; Hodapp, A., and Goldsworthy, E.: Effect of Anticoagulants on Sedimentation Rate, ibid. **190**:775 (Dec.) 1935.

with potassium oxalate. In agreement with Bannick, Gregg and Guernsey [15a] and with Cutler, Park and Herr,[16] it was believed that correction for anemia was unnecessary. No cases of marked anemia were included in the study.

In all but a few cases two or more observations of the sedimentation rate and of the nonfilament-filament ratio were made, and the average was calculated. This tended to minimize any increase in the sedimentation rate due to apprehension or excitement at the time of the initial examination.[17] If the initial readings had

Statistical Analysis of Nonfilament-Filament Ratios and Sedimentation Rates Distributed According to Sex, Age, Disease and Severity of Symptoms *

Group	Nonfilament-Filament Ratio, %				Sedimentation Rate, Mm.				
	No.	Median	Mean	S. D.	S. E.	No.	Median	Mean	S. D.	S. E.
All patients	270	22.50	25.20	10.79	0.657	262	12.10	15.90	13.85	0.857
Sex										
Female	173	22.36	25.74	11.42	0.906	168	14.73	17.52	13.38	1.014
Male	97	21.89	24.60	10.32	1.081	93	7.56	13.24	14.51	1.501
Age										
1-10	17	25.50	26.53	12.10	2.94	10	15.50	15.50	10.08	3.19
11-20	23	26.05	29.09	15.77	3.29	15	10.50	16.00	14.69	3.79
21-30	45	21.57	22.56	8.48	1.26	41	5.50	9.10	8.92	1.39
31-40	52	21.33	25.21	11.33	1.57	54	12.44	16.52	14.80	2.08
41-50	72	21.97	23.42	8.60	1.13	68	12.25	14.47	11.41	1.38
51-60	37	21.50	28.68	13.00	2.14	35	14.66	19.71	17.31	2.90
61+	23	25.50	26.48	13.14	2.74	24	20.14	25.92	16.20	3.31
Severity of symptoms										
Mild	116	18.19	18.56	4.82	0.448	119	6.09	7.20	4.72	0.433
Moderate	98	23.45	24.22	6.47	0.654	88	20.59	19.99	9.36	0.99
Severe	36	38.71	40.10	10.94	1.82	34	35.22	39.91	15.69	2.78
Acutely exacerbated	20	42.58	44.00	10.46	2.34	20	8.42	9.50	6.92	1.55
Disease										
Sinusitis	135	22.61	25.43	11.33	0.972	131	10.90	14.88	12.47	1.09
Nasopharyngitis	122	21.80	24.39	10.02	0.906	120	14.17	17.37	14.62	1.34
Recurrent colds	119	23.09	26.18	11.47	1.027	111	10.40	14.81	12.87	1.25
Tonsillitis	19	24.50	29.05	12.96	2.96	19	18.00	21.16	17.53	4.02
Oral infections	15	19.07	19.33	4.66	1.20	16	16.00	14.25	10.79	2.70
Bronchitis	49	24.67	25.86	8.57	1.22	40	16.00	17.12	14.87	2.35
Gastrointestinal symptoms	37	23.50	24.86	10.78	1.79	30	9.11	13.84	13.97	2.56
Colitis	37	29.50	31.38	13.12	2.16	28	10.22	17.11	16.45	3.12
Biliary	71	22.00	22.79	8.83	1.036	71	9.71	13.35	11.82	1.40
Urinary infection	31	25.50	27.84	12.32	2.22	34	19.67	19.47	13.08	2.24
Rheumatoid arthritis	14	36.75	36.93	16.33	4.37	15	33.00	37.33	18.34	4.74
Other arthritis	24	21.75	24.67	11.97	2.45	25	16.50	16.40	9.67	1.93
Rheumatism	36	21.33	24.38	10.94	1.82	32	10.25	15.97	13.98	2.47
Duodenal ulcer	18	19.68	22.16	7.50	1.77	17	7.17	8.89	7.33	1.78
Asthma	16	24.87	25.50	9.51	2.38	15	10.50	14.33	10.08	2.60

* No. indicates number of cases; S. D., standard deviation; S. E., standard error; biliary, symptoms referable to the biliary tract.

been used, the means and the ranges would have been considerably higher. A similar condition was found in regard to the nonfilament-filament ratio, although it has been said that the nuclear count is not affected by excitement.[18]

16. Cutler, J. W.; Park, F. R., and Herr, B. S.: The Influence of Anemia on Blood Sedimentation, Am. J. M. Sc. **195**:734 (June) 1938.

17. van Antwerp, L. D.: Repeated Sedimentation Tests, Am. J. Dis. Child. **48**: 814 (Oct.) 1934. Cutler, J. W., and Cohen, L.: The Blood Sedimentation Test as a Routine Procedure in the Tuberculosis Dispensary, Am. Rev. Tuberc. **21**:347 (March) 1930.

18. Katz, H. L., and Nice, L. B.: The Relation of the Nonfilament and Filament Counts During Excitement, J. Lab. & Clin. Med. **21**:1145 (Aug.) 1936.

RESULTS

The frequency distributions of the sedimentation rates and nonfilament-filament ratios for all cases are shown in chart 1. Nonfilament-filament ratios ranged from 8 to 70, with a mean of 25.2. Sedimentation rates ranged from 2 to 80 mm., with a mean of 15.9 mm. Median

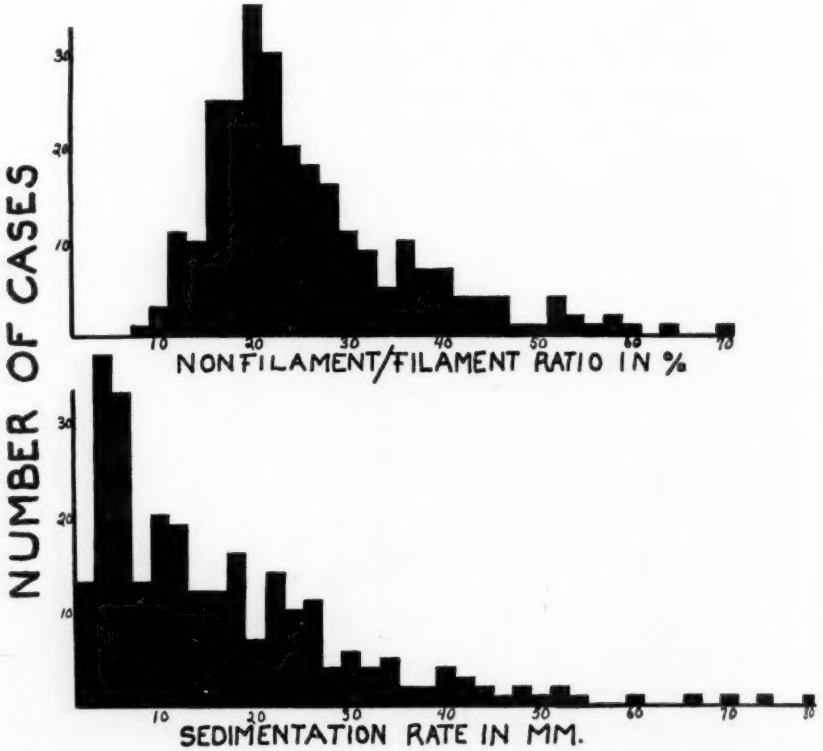

Chart 1.—Frequency distribution of nonfilament-filament ratios and sedimentation rates for all cases.

and mean values, with standard deviations and standard errors, are recorded in the table.

When the observations were distributed according to sex (chart 2), the mean sedimentation rate for females was 17.52 mm., as compared with 13.24 mm. for males, the difference being 2.68 times its standard error. There was no significant difference in the nonfilament-filament ratios.

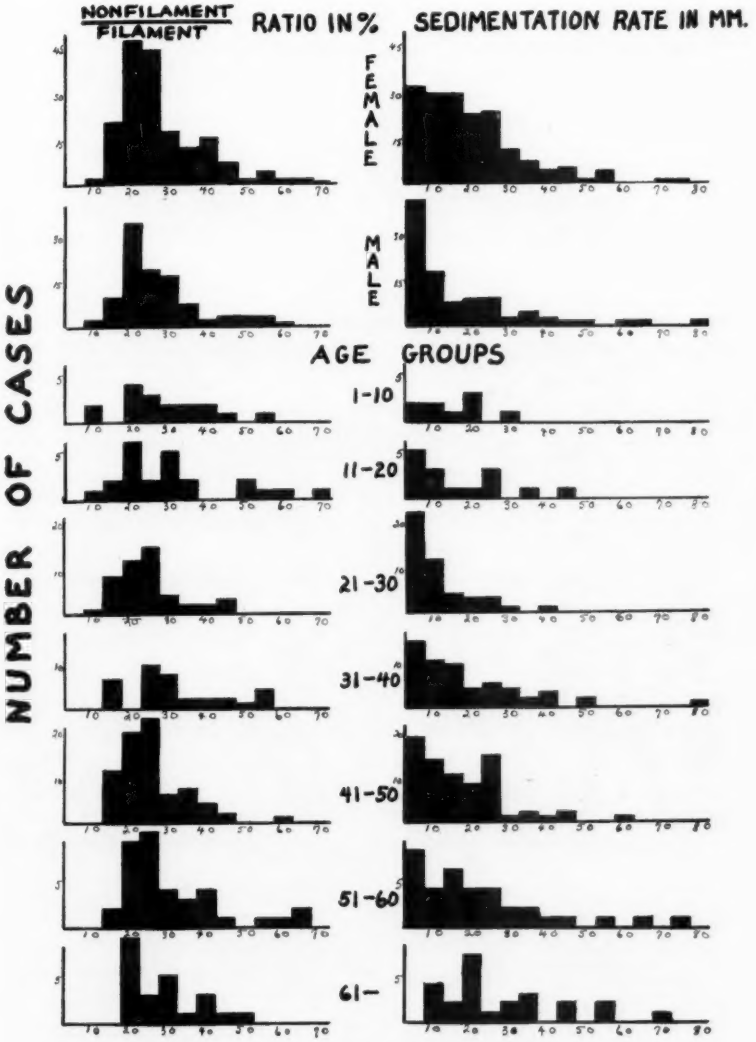

Chart 2.—Nonfilament ratios and sedimentation rates distributed according to sex and age.

When distributed according to age (chart 2), the mean nonfilament-filament ratios showed some variation, but in no case did the mean for any group differ from the mean for all cases by as much as 2.5 times the standard error of the difference. Sedimentation rates showed a somewhat greater variation. The mean for the group aged 21 to 30

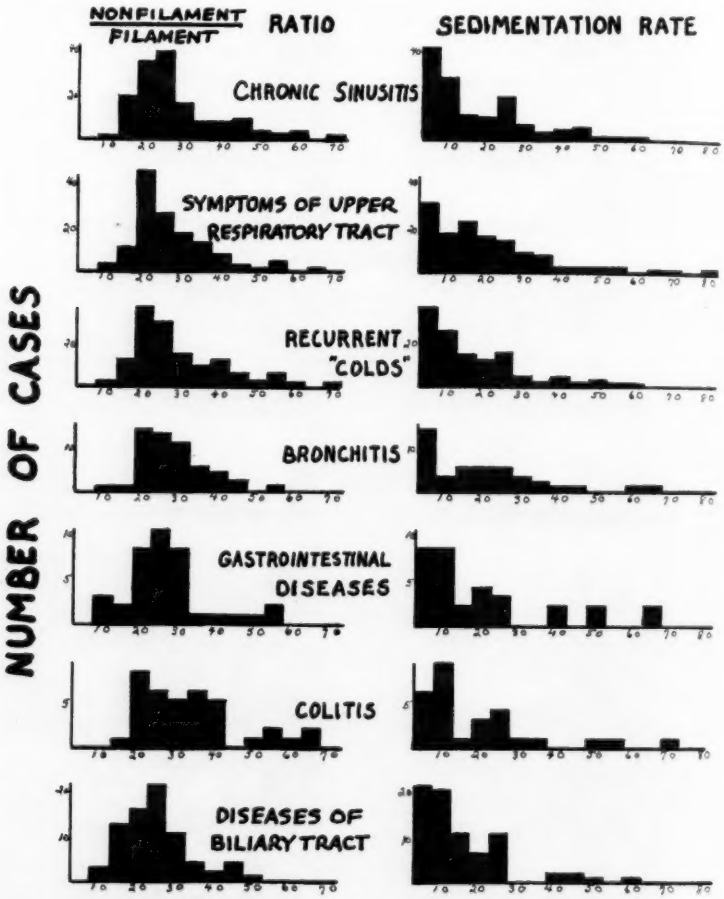

Chart 3.—Nonfilament-filament ratios and sedimentation rates in cases of sinusitis, nasopharyngitis (symptoms of the upper respiratory tract), recurrent colds, bronchitis, colitis, other gastrointestinal diseases and diseases of the biliary tract.

years was 9.1 mm. (table), the difference from the mean for all cases being 4.53 times its standard error. The mean for the group over 60

was 25.9 mm., the difference from the mean of the entire series being five times its standard error. These differences were probably due less to age than to other factors which will be discussed later.

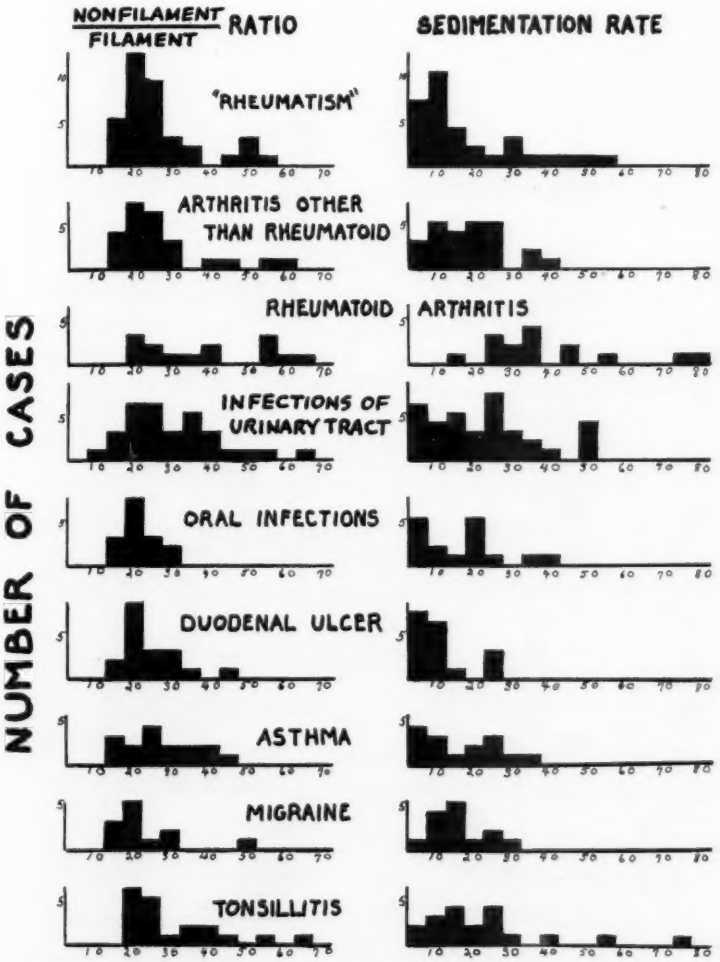

Chart 4.—Nonfilament-filament ratios and sedimentation rates in cases of "rheumatism," rheumatoid arthritis, other forms of arthritis, infections of the urinary tract, oral infections, duodenal ulcer, asthma, migraine and tonsillitis.

When the findings were distributed according to disease (charts 3 and 4), in cases of sinusitis, nasopharyngitis, recurrent colds, bronchitis, gastrointestinal conditions other than colitis, symptoms referable to the

biliary tract, infections of the urinary tract, prostatitis, rheumatism, arthritis other than the rheumatoid form and asthma, there were no significant differences from the general averages. In cases of tonsillitis, infection of the ear and mastoid and migraine there were minor devia-

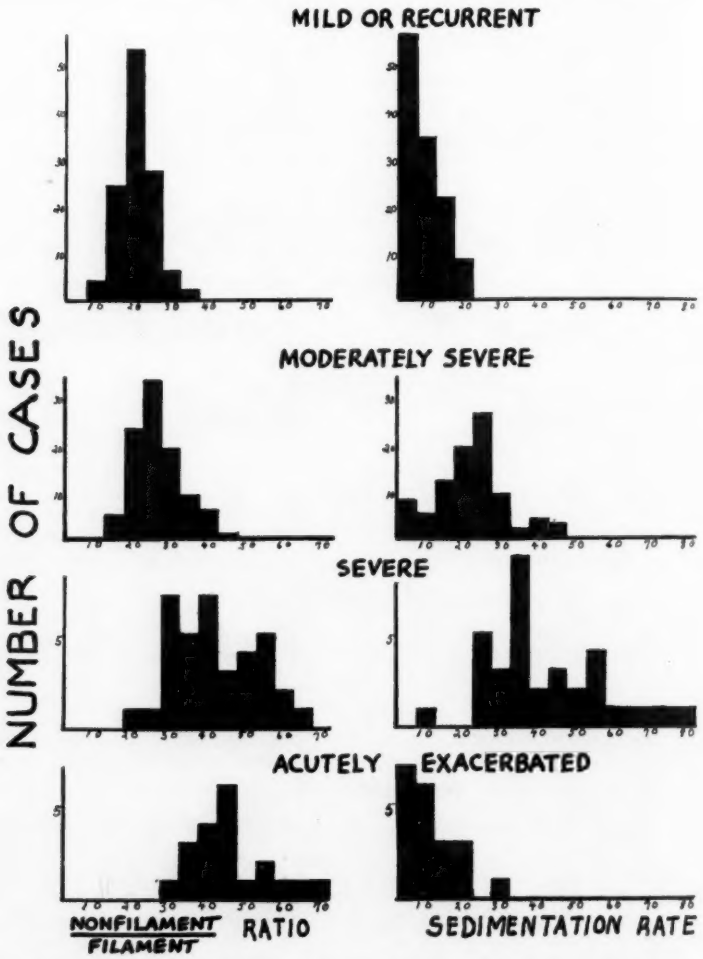

Chart 5.—Nonfilament-filament ratios and sedimentation rates distributed according to severity of symptoms.

tions from the general averages, but in no group was the number of cases sufficiently large or the deviation great enough to justify making positive inferences. In cases of oral infection (chart 4) the mean non-

filament-filament ratio was less than the mean for all cases by 4.31 times the standard error, but there was no significant variation in the sedimentation rate. In cases of colitis (chart 3) the mean nonfilament-filament ratio was 31.38, the difference from the mean of the entire series being 3.68 times the standard error, but again there was no significant difference in the sedimentation rate. In cases of duodenal ulcer (chart 4) the mean sedimentation rate was lowest (8.98 mm.), the difference from the mean for all cases being 4.32 times its standard error. The mean nonfilament-filament ratio was 22.16, the difference from the general mean being 1.93 times its standard error.

In cases of rheumatoid arthritis (chart 4) there were significant increases. The mean nonfilament-filament ratio was 36.93, the difference from the general mean being 5.23 times its standard error. The mean sedimentation rate was 37.33 mm., the difference from the general mean being 9.1 times the standard error.

When the findings were distributed according to severity of symptoms (chart 5) significant differences were found. When symptoms were mild or recurrent the mean nonfilament-filament ratio was 18.56 (116 cases) and the mean sedimentation rate 7.2 mm. (119 cases). When symptoms were of moderate severity the mean nonfilament-filament ratio was 24.22 (98 cases) and the mean sedimentation rate 19.99 mm. (88 cases). When symptoms were severe the mean nonfilament-filament ratio was 40.1 (36 cases) and the mean sedimentation rate 39.91 mm. (34 cases). In an additional 20 cases the symptoms at the time of examination were more or less acutely exacerbated. In these cases the mean nonfilament-filament ratio was 44 and the mean sedimentation rate 9.5 mm.

COMMENT

The values which have been used as normal standards for the nuclear count and the sedimentation rate vary considerably. Schilling's [19] values for the nuclear count, 64 per cent segmented neutrophils and 4 per cent young forms, which have been widely used, e. g., by Crocker and Valentine,[20] in their extensive studies, and by Nicolle,[21] Black,[22] Gorsky,[23]

19. Schilling, V.: The Blood Picture and Its Clinical Significance, St. Louis, C. V. Mosby Company, 1929.

20. Crocker, W. J.; Valentine, E. H., and Brody, W.: Hemography-Controlled Nonspecific Immunotransfusions in the Treatment of Septicemia and Other Acute Infections, J. Lab. & Clin. Med. **20**:482 (Feb.) 1935. Crocker and Valentine (footnotes 7 and 10).

21. Nicolle, H. J.: The Schilling Index, New Orleans M. & S. J. **84**:114 (Aug.) 1931.

22. Black, W. C.: Schilling's Differential Count, Colorado Med. **27**:189 (June) 1930.

23. Gorsky, S.: Interpretation of the Leucocyte Differential Count and the Schilling Nuclear Shift in the Blood, M. J. & Rec. **135**:468 (May 18) 1932.

Short and associates,[24] Finney and Dunlop,[25] Niehaus [26] and Steinberg,[27] are consistent with the results of Osgood's [28] recent studies on normal subjects. Further, Schilling's value for young forms is only slightly less than Cooke and Ponder's [29] value for their class I cells (nonfilamented), and his value for segmented cells approximates that for Cooke and Ponder's combined classes II, III, IV and V (filamented), provided Cooke and Ponder's values are expressed in percentages of the total leukocyte count. In the present study Schilling's values were used, which means that any nonfilament-filament ratio over 7 was considered abnormal. On this basis all the patients for whom counts were made had abnormal ratios, which is in agreement with Griffith's [6] findings in cases of focal infection.

In regard to the sedimentation rate, Westergren [30] called values up to 3 mm. normal and values from 4 to 6 mm. doubtful. Beaumont and Maycock,[31] Kilduffe,[32] Schulten [3] and Hirsh [33] mentioned similar normal standards, although all except Beaumont and Maycock gave a higher normal value for females than for males. In the present study Kilduffe's normal values of 3 mm. for males and 5 mm. for females were adopted as standards. By these standards 87 per cent of the males and 82 per cent of the females had rates above normal.

Thus it appears that the sedimentation rate is not as sensitive an indicator of minor variations in health as is the nonfilament-filament ratio, which showed abnormal values for all patients. Of patients with mild symptoms, 34 per cent had normal sedimentation rates (4 mm. being used as the normal limit when rates were not distributed according

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24. Short, C. L.; Dienes, L., and Bauer, W.: Rheumatoid Arthritis: A Comparative Evaluation of the Commonly Employed Diagnostic Tests, J. A. M. A. **108**:2087 (June 19) 1937.

25. Finney, R. H., and Dunlop, J. N.: The Schilling Blood Count, Colorado Med. **30**:212 (June) 1933.

26. Niehaus, F. W.: Value of Leucocyte Counts According to Arneth-Schilling Formula in Clinical Medicine, M. Clin. North America **12**:395 (Sept.) 1928.

27. Steinberg, C. L.: The Schilling Count in Fifty-Nine Cases of Rheumatoid Arthritis, Am. J. M. Sc. **190**:98 (July) 1935.

28. Osgood, E. E.: Normal Hematologic Standards, Arch. Int. Med. **56**:849 (Nov.) 1935.

29. Cooke, W. E., and Ponder, E.: The Polynuclear Count, Philadelphia, J. B. Lippincott Company, 1927.

30. Westergren, A.: On the Stabilitary Reaction of the Blood in Pulmonary Tuberculosis, Brit. J. Tuberc. **15**:72 (April) 1921.

31. Beaumont, G. E., and Maycock, J. W.: The Erythrocyte Sedimentation Rate, Lancet **2**:19 (July 6) 1935.

32. Kilduffe, R. A.: The Clinical Interpretation of Blood Examinations, Philadelphia, Lea & Febiger, 1931, p. 115.

33. Hirsh, J. E.: The Value of the Sedimentation Test as a Diagnostic Aid, Ann. Int. Med. **10**:495 (Oct.) 1936.

to sex), but only 1 had a nonfilament-filament ratio below 10. When the symptoms were moderate, 6 per cent of the patients had normal sedimentation rates, while the lowest nonfilament-filament ratio was 12. When the symptoms were severe there were no normal observations, the lowest sedimentation rate being 9 mm. and the lowest nonfilament-filament ratio 18. When symptoms were acutely increased the nonfilament-filament ratio was elevated to a much greater extent than the sedimentation rate. The greater sensitiveness of the nonfilament-filament ratio in arthritis has been commented on by Steinberg [27] and in tuberculosis by Leitner [34] and Thiele.[35]

While the nonfilament-filament ratio is the more prompt indicator of changes in the activity of a disease process, it is generally agreed that the sedimentation rate tells more regarding fundamental changes in disease.[36] When remission occurs in a chronic infection the nonfilament-filament ratio falls, but the sedimentation rate remains elevated for a considerable time, a warning that body conditions have not returned to normal. In view of the readiness with which the nonfilament-filament ratio responds to acute exacerbations, it appears that an increased sedimentation rate would have greater significance in the diagnosis of chronic infection than would an increased nonfilament-filament ratio. For example, Sjögren [5] found the sedimentation rate more useful than the white blood cell count in the diagnosis of latent ocular infection.

The difference in sedimentation rate between the sexes was chiefly in values lying between the normal limits and 30 mm. Approximately equal percentages of males and females had normal rates or rates above 30 mm. When the abnormal rates under 30 mm. were analyzed, the mean for females was 15.28 mm. and the mean for males 10.7 mm. While the numerical difference between these means is no greater than that when all cases were included, the significance is greater (3.72 times the standard error).

When the findings were grouped according to age, the 21 to 30 year group showed a low sedimentation rate (9.1 mm.), probably due not to any factor associated with age but to the fact that in this particular group there was a high percentage of cases in which the symptoms were mild. The high mean sedimentation rate found in the group of patients over 60 may have been due partly to the effect of age but was apparently

34. Leitner, J.: Significance of White Blood Picture in Its Relationship to Sedimentation Speed of Erythrocytes in Clinical Evaluation of Some Forms of Pulmonary Tuberculosis, Beitr. z. Klin. d. Tuberk. **86**:297 (June 25) 1935.

35. Thiele, G.: Significance of White Blood Picture in Relation to Sedimentation Speed of Erythrocytes in Clinical Estimation of Some Forms of Pulmonary Tuberculosis, Beitr. z. Klin. d. Tuberk. **86**:126 (March 23) 1935.

36. Blood Sedimentation Tests, Queries and Minor Notes, J. A. M. A. **108**: 577 (Feb. 13) 1937.

due chiefly to the presence in this group of an unusually high number of patients with severe symptoms.

When grouped according to the diagnosis, the findings in only a few diseases showed significant differences from the general averages. In colitis the mean nonfilament-filament ratio was significantly above the general average, although the mean sedimentation rate was not affected. The figures reported here are much lower than those reported by Garvin and Bargen [1] in cases of ulcerative colitis, as would be expected in view of the fact that only a few cases of ulcerative colitis, in all of which the disease was quiescent, were included in the present series.

In cases of duodenal ulcer the mean sedimentation rate was significantly lower than the general average. This is in keeping with Schindler and Gnagi's [4] finding that the sedimentation rate is low in cases of uncomplicated peptic ulcer.

Patients with rheumatoid arthritis showed a mean nonfilament-filament ratio and mean sedimentation rate significantly above the general averages. The mean sedimentation rate was not as high as that reported by Bannick and his associates [15a] (71.6 mm.), but was close to that reported by Rawls and his associates [37] and by Forestier.[38] A considerable variation in the means reported by various authors might be explained by differences in the severity of the disease. The increase in the nonfilament-filament ratio is in general agreement with the increased nonfilamented cell counts reported in cases of rheumatoid arthritis by Steinberg,[27] Hartung and his associates,[39] Steinbrocker and Hartung [40] and Rawls and his associates,[37] although the mean nonfilamented cell counts reported by Steinbrocker and Hartung [40] and by Hartung and his co-workers [39] were relatively higher than the mean of the present series.

The mean sedimentation rate in "rheumatism" was somewhat higher than that reported by Bannick and his associates [15a] in fibrositis (11.6 mm.) and did not agree with Schulten's [3] finding of a "normal" sedimentation rate in muscular rheumatism.

In general, detailed study of the cases reported gave the impression that the sedimentation rate and the nonfilament-filament ratio varied primarily with the severity of symptoms, rather than with the type of disease. For example, patient 93, with quiescent rheumatoid arthritis,

37. Rawls, W. B.; Gruskin, B. J.; Ressa, A. A., and Jordan, M.: The Sedimentation Rate and Polymorphonuclear Count in Rheumatoid and Mixed Arthritis, J. Lab. & Clin. Med. **19**:830 (May) 1934.

38. Forestier, J.: The Treatment of Rheumatoid Arthritis with Gold Salts Injections, Lancet **1**:441 (Feb. 27) 1932.

39. Hartung, E. F.; Davis, J. S.; Steinbrocker, O., and Straub, M. E.: The Blood in Arthritis, J. A. M. A. **106**:1448 (April 25) 1936.

40. Steinbrocker, O., and Hartung, E. F.: The Filament-Nonfilament Count in Chronic Arthritis, J. A. M. A. **100**:654 (March 4) 1933.

had a sedimentation rate of 13 mm. and a nonfilament-filament ratio of 20, while patient 263, with chronic sinusitis and "rheumatism," had a sedimentation rate of 51 mm. and a nonfilament-filament ratio of 30.

These observations add confirmation to the many reports which have endorsed the earlier findings by Westergren,[30] Schilling [19] and Cooke and Ponder [29] that the sedimentation rate and the polymorphonuclear count are useful in determining the severity of disease, in following its progress and in judging the value of treatment.

SUMMARY

Observations on the sedimentation rate and nuclear count were made on 292 patients with chronic or frequently recurring symptoms which were suspected of being secondary to low grade chronic infection. Of this number 277 showed evidence of either chronic sinusitis or chronic nasopharyngitis. There were 52 patients with chronic bronchitis, 75 with symptoms referable to the biliary tract, 78 with gastrointestinal conditions, 36 with symptoms referable to the urinary tract, 40 with arthritis and 36 with "rheumatism."

The mean sedimentation rate (Westergren) for all patients was 15.9 mm.; the mean nonfilament-filament ratio ($\frac{\text{nonfilamented neutrophils} \times 100}{\text{filamented neutrophils}}$) was 25.2. The mean sedimentation rate for females was higher than that for males, but there was no variation in the nonfilament-filament ratio. There were no significant variations when the sedimentation rates and nonfilament-filament ratios were distributed according to age, except for a possibly significant increased sedimentation rate in the group of patients over 60. When the findings were distributed according to disease there were only questionable variations, except for colitis (high nonfilament-filament ratio), duodenal ulcer (low sedimentation rate) and rheumatoid arthritis (high sedimentation rate and nonfilament-filament ratio).

When the findings were distributed according to severity of symptoms, there was a direct relationship: As symptoms increased the sedimentation rate and nonfilament-filament ratio increased. When symptoms were more or less acutely exacerbated the nonfilament-filament ratio was high, but the sedimentation rate was relatively low.

According to Schilling's, Cooke and Ponder's or Osgood's criteria for normal neutrophilic distribution, the nonfilament-filament ratio was increased above normal in practically all cases. According to Kilduffe's normal limits of 3 mm. for males and 5 mm. for females, more than 80 per cent of the sedimentation rates observed were abnormal.

On the basis of these findings, the nonfilament-filament ratio appears to be a more sensitive indicator of the presence of disease than the sedimentation rate, although the readiness of its response to acute exacer-

bation makes the finding of an increased sedimentation rate of more significance in the diagnosis of chronic illness than the finding of an increased nonfilament-filament ratio.

CONCLUSIONS

Practically all of a group of 292 patients with symptoms of low grade chronic disease showed an increase in the nonfilament-filament ratio, while more than 80 per cent showed an increased sedimentation rate.

The sedimentation rate and nonfilament-filament ratio showed only minor variations when distributed according to age, sex or diagnosis. When distributed according to the intensity of symptoms they showed a direct relationship to increases in the severity of illness.

These findings should prove useful in following the course of low grade chronic disease and in evaluating treatment.

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EVALUATION OF THE CONCENTRATION OF SERUM SULFATE

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In 1931 we [1] recorded data on the concentration of serum sulfate and of blood urea in cases of renal insufficiency of varying degrees. At that time we stated specifically that the concentration of serum sulfate may be increased in a case of early renal insufficiency while the concentration of blood urea is within normal limits. However, we now believe this fact may be more precisely stated by saying that the concentration of serum sulfate may exceed the normal limits in cases of mild, rather than early, renal insufficiency. When there is definite renal insufficiency, the concentrations of both blood urea and serum sulfate will usually be increased. Why the value for serum sulfate is increased when the concentration of blood urea is normal is a phenomenon we cannot explain. The functional activity of the kidney is so complex, however, that a moderate increase of any one substance in the serum or blood should not be used implicitly as an index of the functional ability of this organ. In fact, clinical experience has proved that physicians should not depend too greatly on prognostic data that are obtained from the most comprehensive tests of renal function. Any test of renal function at times may indicate good kidneys, and yet the patient, if subjected to a serious operation, may succumb to renal failure immediately afterward.

Determination whether the concentration of serum sulfate can be used as an index of renal function was not the object of this study, which was rather to find out more about the frequency with which increased concentrations of serum sulfate occur in cases of mild renal insufficiency. The relation that the increase in concentration of serum sulfate has to the decrease in the values obtained by the urea clearance test, to the increase in the concentration of blood urea and to the specific gravity of the urine was our chief concern.

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1. Wakefield, E. G.; Power, M. H., and Keith, N. M.: Inorganic Sulfates in the Serum in Early Renal Insufficiency: Significance of Determinations, J. A. M. A. **97**:913-917 (Sept. 26) 1931.

The method used in determining the concentration of serum sulfate was a modification of Cope's [2] procedure, namely, alkalimetric titration of benzidine sulfate separated from trichloroacetic acid filtrates of serum by means of a solution of benzidine in acetone. The technic has been used by us for several years.[3] In our hands the values obtained by this method for the inorganic sulfate in normal serum have been, as might be expected, somewhat lower than the results of our earlier analyses, in which the benzidine sulfate was oxidized with potassium bichromate. Recently we have found that the use of alcohol in the precipitation of benzidine sulfate from a trichloroacetic acid filtrate is more satisfactory than the use of acetone, although the results obtained by the two methods of precipitation are not greatly divergent and are in reasonable agreement with the results of determinations by the microgravimetric barium sulfate method. A report of our experience with these and other methods for the determination of the concentration of inorganic sulfate in serum has recently been published.[4]

Øllgaard [5] has recently developed a procedure in which the sulfate in precipitates separated from trichloroacetic acid filtrates by benzidine in acetone is titrated with a solution of barium chloride, in the presence of sodium rhodizonate as an indicator. This procedure may possibly be somewhat more specific for sulfate than the alkalimetric titration. The values for serum sulfate obtained by its use, however, appear to be in close agreement with those obtained in this study.

The range of normal values for the concentration of sulfate in the serum was obtained by a study of 125 normal persons, the criteria for their selection being as follows: (1) the clinical absence of evidence of organic disease history and general physical examination; (2) absence of albumin, sugar, casts, pus and blood in the urine; (3) a concentration of blood urea of less than 40 mg. per hundred cubic centimeters, and (4) normal or decreased urea clearance (determined in about half the cases).

The mean value was 3.7 mg. of sulfate (1.23 mg. of sulfur) in 100 cc. of serum, and 95 per cent of the values fell within the range of

2. Cope, C. L.: Determination of Inorganic Sulfate in Human Blood-Plasma by Micro-Titration, Biochem. J. **25**:1183-1189, 1931.

3. Power, M. H.; Wakefield, E. G., and Peterson, R. D.: The Microdetermination of Ethereal Sulfate in Blood Serum, J. Biol. Chem. **105**:lxvii-lxviii (May) 1934.

4. Power, M. H., and Wakefield, E. G.: A Volumetric Benzidine Method for the Determination of Inorganic and Ethereal Sulfate in Serum, J. Biol. Chem. **123**:665-678 (April) 1938.

5. Øllgaard, E.: Undersøgelser blodets vandopløselige svovlforbindelser, Thesis, Copenhagen, Nyt Nordisk Forlag. Arnold Busck, 1937; Eine mikrotitrimetrische Methode zur Bestimmung von Sulfaten im Plasma, Biochem. Ztschr. **274**:181 (Nov. 14) 1934.

2.4 to 4.9 mg. of sulfate (0.80 to 1.63 mg. of sulfur) per hundred cubic centimeters of serum.

In order to obtain proper data, it was necessary to designate certain arbitrary limits of what was to constitute the "normal" and, conversely, the "abnormal." In using the urea clearance test, we therefore chose to designate all values of less than 40 (the number of cubic centimeters of blood cleared of urea per minute when the volume of urine excreted was less than 2 cc. per minute) as below normal, or decreased. All maximum values of less than 60 were considered as indicating a decreased clearance. When the average excretion of urine was less than 0.5 cc. per minute the data were not included. It seemed well to limit further

TABLE 1.—*Relation of Urea Clearance and the Concentration of Serum Sulfate to the Concentration of Blood Urea*

	Serum Sulfate				Urea Clearance			
	Increased		Normal		Decreased		Normal	
Blood Urea	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage
Increased (143 cases)	113	79	30	21	118	82.5	25	17.5
Normal (508 cases)	85	16.7	423	83.3	147	28.9	361	71.1

TABLE 2.—*Relation of Urea Clearance and the Concentration of Blood Urea to the Concentration of Serum Sulfate*

	Blood Urea				Urea Clearance			
	Increased		Normal		Decreased		Normal	
Serum Sulfate	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage
Increased (198 cases)	113	57	85	43	141	71.2	57	28.8
Normal (453 cases)	30	6.6	423	93.4	124	27.4	329	72.6

the group of patients to be studied by omitting all those whose concentration of urea was more than 100 mg. per hundred cubic centimeters of blood. Concentrations of 44 mg. or more of urea in 100 cc. of blood were considered increased. Concentrations of 5 mg. or more of sulfate (1.67 mg. or more of sulfur) in each 100 cc. of serum were considered to be increased.

In tables 1 and 2 are recorded the data obtained from a study of 651 hospital patients who were known to have or were suspected of having renal insufficiency. There were no set clinical criteria for studying these patients except that the obtaining of further data on renal function was indicated. On the morning of the tests the patient was kept in bed. The urea clearance test was performed in duplicate periods. As indicated in table 1, the concentration of blood urea was

increased in 143 cases and was normal in 508 cases. The values for serum sulfate were increased in 79 per cent and normal in 21 per cent of the cases in which the concentration of blood urea was increased and increased in 16.7 per cent of the 508 cases in which the concentration of blood urea was normal. It is this 16.7 per cent of cases in which the concentration of serum sulfate was increased that has been of interest to us. We believe that this series is large enough to corroborate our original contention that an increased concentration of serum sulfate may occur while the concentration of blood urea remains within normal limits. That mild renal insufficiency was present in some of the 16.7 per cent of cases was proved by the subsequent course. The decrease in the clearance of urea and the increase in the concentration of serum sulfate did not always parallel each other. This fact is demonstrated in tables 1 and 2, which show that increased concentrations of serum sulfate occurred in 198 of the 651 cases and that a decreased clearance of urea occurred in only 141, or 71.2 per cent, of the 198 cases. Whereas the clearance of urea was decreased in 27.4 per cent of cases in which the concentration of serum sulfate was normal, it was not altered in 28.8 per cent of the cases in which the concentration was increased.

The urea clearance test, when properly employed as a test of renal function, is repeated at intervals; it is the general trend of the results of any test which indicates its prognostic significance. This fact also should be true of the concentration of blood urea or the specific gravity of the urine when they are used as indicators of renal function. In our practice it is not practical, and is often not possible, to employ the urea clearance test in this way. However, in cases of nephritis in which increasing azotemia and a decrease in the concentration of hemoglobin occur the test alone often furnishes a satisfactory prognosis.

We believe with many other observers that in the absence of large amounts of albumin in the urine (grade 2 or less, on a basis of 4) the specific gravity of the urine is an excellent indicator of renal function. Under most circumstances, when the renal lesion is not acute, as it is in acute glomerulonephritis, kidneys which excrete urine of a specific gravity of 1.025 or more may be considered good. Tables 3 and 4 contain data obtained in 100 cases under circumstances similar to those observed in tables 1 and 2, except that in all the cases in tables 3 and 4 the specific gravity of a twelve hour specimen of urine was 1.025 or greater. To check the increased concentration of serum sulfate and the urea clearance against the specific gravity of a twelve hour specimen of urine when this was 1.025 or more would furnish some idea of the probable influence of a low intake of fluid on the results of the tests. It will be seen that an increased concentration of blood urea occurred

in 41 of the 100 cases. In all these cases the values were less than 60 mg. per hundred cubic centimeters. The concentration of serum sulfate was increased in 25 cases and normal in 75 cases. In 51.2 per cent of cases in which the blood urea was increased the serum sulfate also was increased. In 84 per cent of cases in which the concentration of serum sulfate was increased the concentration of blood urea also was increased. The results obtained with the urea clearance test indicated the same general trend; in 56 per cent of cases in which the blood urea was increased, the urea clearance was decreased. When the data obtained for the 100 patients in tables 3 and 4 are separated on the

TABLE 3.—*Relation of Urea Clearance and the Concentration of Serum Sulfate to the Concentration of Blood Urea in 100 Cases in Which the Specific Gravity of the Urine was 1.025 or Higher*

	Serum Sulfate				Urea Clearance			
	Increased		Normal		Decreased		Normal	
Blood Urea	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage
Increased (41 cases)	21	51.2	20	48.8	23	56	18	44
Normal (59 cases)	4	6.8	55	93.2	46	78	13	22

TABLE 4.—*Relation of Urea Clearance and the Concentration of Blood Urea to the Concentration of Serum Sulfate in 100 Cases in Which the Specific Gravity of the Urine was 1.025 or Higher*

	Blood Urea				Urea Clearance			
	Increased		Normal		Decreased		Normal	
Serum Sulfate	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage
Increased (25 cases)	21	84	4	16	18	72	7	28
Normal (75 cases)	20	26.6	55	73.3	51	68	24	32

basis of increased or decreased values for the concentration of serum sulfate, it is found that in 84 per cent of cases in which the concentration was increased the blood urea also was increased. The urea clearance was decreased in 72 per cent of cases in which the serum sulfate was increased. In brief, these data indicate that a low fluid intake seems more readily to affect the concentration of blood urea than it does the urea clearance or the concentration of serum sulfate.

That a low fluid intake does not readily affect the concentration of serum sulfate has been demonstrated by study of the concentrations of this substance in cases in which urinary obstruction was produced by hypertrophy of the prostate gland and cases of pyloric obstruction associated with dehydration. In such cases the concentration of urea

may reach 100 mg. per hundred cubic centimeters of blood while the concentration of serum sulfate remains normal.

In our experience, gained by determining the concentration of serum sulfate in cases of known and suspected renal insufficiency, the conclusion that an increased concentration of sulfate is associated with failure of renal function is reasonable. The concentration of serum sulfate may be increased in renal insufficiency when that of blood urea is normal. This study illustrates that when the patient has definite renal insufficiency all the tests of so-called renal function will indicate its presence. However, if there is uncertainty as to the status of renal function, the results obtained with any one functional test may vary greatly if the test is repeated often. Therefore, if a number of these tests are conducted synchronously, as has been done in this study, variations in the results are to be expected.

In a report which we made in 1931 on the concentration of sulfate in the serum we said that it had been observed to reach unpredictable heights. Since 1931 we have repeatedly confirmed this observation. In 1 case in which the concentration was high we were able to check the results obtained with the titration method by using the gravimetric method to determine the amount of sulfate in the filtrate of 50 cc. of serum. In several cases in which the concentration of serum sulfate was high studies of the acid base equilibrium have been made in order to check our method of determining the concentration of sulfate in the serum. For instance, in 1 case the concentration of sulfate was 16.2 milliequivalents per liter of serum. The concentration of total determined acids plus base protinate was 146.3 milliequivalents per liter of serum (chlorides 95.7, bicarbonate 11.2, phosphates 6.9, sulfate 16.2, lactic acid 0.6 and base protinate 15.7), and the concentration of total base was 151.4 milliequivalents per liter of serum (sodium, 140; potassium, 6; calcium, 3.1, and magnesium, 2.3). A concentration of 20 milliequivalents of sulfate per liter of serum can and actually does occur; when it does, the patient suffers from uremic acidosis and has been suffering from nausea and vomiting for days, usually for a fortnight. There may be a marked decrease in the concentration of chlorides in the plasma and in the carbon dioxide–combining power of the plasma.

SUMMARY

Ninety-five per cent of the values for the concentration of serum sulfate in normal persons ranged from 2.4 to 5 mg. (0.8 to 1.67 mg. of sulfur) per hundred cubic centimeters. It was increased for 16.7 per cent of patients suspected of having mild renal insufficiency, while the concentration of blood urea was within normal limits. The blood urea was increased for 6.6 per cent of patients who had normal concentra-

tions of serum sulfate, an association seemingly related to low intake of fluid and, according to present data, a favorable prognostic indication. Urea clearance tests, when performed under the conditions described in this study, vary widely. In so-called uremic acidosis, concentrations of serum sulfate may reach unpredictable heights. We have observed concentrations of 20 milliequivalents in cases in which the concentration of chlorides and the carbon dioxide–combining power of the plasma were reduced.

MASCULINOVOBLASTOMA

PRIMARY MASCULINIZING TUMOR OF THE OVARY (SO-CALLED LARGE CELL VARIETY—HYPERNEPHROID—LUTEOMA)

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Two nonrelated ovarian tumors associated with masculinization are now described, the arrhenoblastoma and a large cell type variously called hypernephroma, hypernephroid and luteoma. The reason for the variety of names for the latter growth is the imperfect knowledge of its histogenesis, some authors favoring its origin from an adrenal rest and others from lutein elements. The first report to appear in the literature was that of Bovin.[1] Glynn [2] in 1917 criticized inclusion of the tumor among ovarian growths, on the ground that it lay in the broad ligament and not primarily in the ovary.

Other reports of growths at first included in this group but later discarded followed. Thus Tuffier [3] reported a case in which the diagnosis was primary adrenal tumor with metastasis to the ovary, while Cosacesco and his associates [4] classified the lesion as *lutéinome*. However, the presence of large bilateral adrenal masses as well as the ovarian growth renders the case unacceptable. Büttner [5] described a tumor composed of tubules and lipoid-containing cells, a combination representing, as he concluded, a transition form between the arrhenoblastoma and the so-called hypernephroid. Meyer [6] expressed the belief that it should be

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1. Bovin, E.: Ueber im weiblichen Genitale primär entstandene hypernephroide Geschwülste, Nord. med. Ark. **15**:1, 1908; Des tumeurs hypernéphroïdes primitives des organes génitaux feminins, Semaine méd. **30**:66, 1910.

2. Glynn, E.: A Comparison Between Ovarian "Hypernephroma" and Luteoma and Suprarenal Hypernephroma, with Comments on Suprarenal Virilism, J. Obst. & Gynaec. Brit. Emp. **28**:24, 1921.

3. Tuffier, C.: La virilism surrenal, Bull. Acad. de méd., Paris **30**:726, 1910.

4. Cosacesco, A.; Draganescu, S.; Georgescu, M., and Dinischiotu, G. T.: Lutéinome de l'ovaire: Contribution anatomo-clinique à l'étude du virilisme ovarien, Presse méd. **68**:1264, 1931.

5. Büttner, A.: Ueber Eierstockgeschwülste mit Vermännlichung, Virchows Arch. f. path. Anat. **287**:452, 1932.

6. Meyer, R., cited by Benecke, E.: Zur Frage der Vermännlichungsgeschwülste des Eierstockes nebst Mitteilung von zwei neuen Fällen, Virchows Arch. f. path. anat. **294**:38, 1934.

classified in the latter group, while Schiller [7] stated that the presence of tubules placed it in the former. The case reported by Parhon and Aburel [8] has likewise been discarded, on the ground that the ovarian tumor was multicystic and further that there was insufficient evidence to warrant classifying it in any particular group. Thus when Novak and Wallis [9] added their report, there were only 3 acceptable cases (those of Cosacesco and his associates,[4] Sellheim [10] and Bingel [11]), theirs making a fourth. Since then Saphir and Parker [12] and Maxwell [13] have published reports of cases. Saphir and Parker called the lesion in their case an example of adrenal rest in the ovary and concluded that it was different from the tumor in question. Yet, aside from size, we could see no microscopic differences between it and the others referred to. Maxwell [13] reported her case as an instance of arrhenoblastoma. Schiller [14] expressed the opinion that it belonged to the so-called hypernephroid group instead.

REVIEW OF CASES REPORTED IN THE LITERATURE

Bovin's [1] Case.—The patient, a 28 year old woman, first came under observation in September 1907. At the age of 21 there had been cessation of menstrual periods, accompanied a year later by hirsutism, which gradually became pronounced until she found it necessary to shave regularly. Further, there was persistent abdominal pain, gradually becoming worse.

On physical examination she appeared to be well built and had an abundant growth of hair about the face and abdomen. Development of the breasts was normal. On vaginal examination a movable mass, about the size of a fist, was felt to the left of and behind the uterus. The right side appeared normal.

At operation, in March 1908, a nonpedunculated tumor was found on the left side, in the pouch of Douglas. The fallopian tube lay free on its upper surface. The right ovary was small and sclerotic.

Two and one-half months postoperatively the menstrual periods returned and recurred regularly thereafter. At the last notation, on Aug. 9, 1909, one and

7. Schiller, W., cited by Novak and Wallis.[9]

8. Parhon and Aburel, cited by Cosacesco, Draganescu, Georgescu and Dinischiotu.[4]

9. Novak, J., and Wallis, O.: Vermännlichung und Wiederverweiblichung (Beitrag zur Kenntnis der "Luteinzellentumoren" des Ovariums), Arch. f. Gynäk. **164**:543, 1937.

10. Sellheim, H.: Vermännlichung und Wiederverweiblichung bei einem ausgewachsenen Individuum, Ztschr. f. mikr.-anat. Forsch. **3**:382, 1925.

11. Bingel, A.: Verschwinden von Polycythämie und Rückbildung von Vermännlichung noch Entfernung eines Luteinzellentumors, Deutsche med. Wchnschr. **50**:330, 1924.

12. Saphir, W., and Parker, M. L.: Adrenal Virilism, J. A. M. A. **107**:1286 (Oct. 17) 1936.

13. Maxwell, A. F.: Masculinizing Tumors of the Ovary, West. J. Surg. **45**: 134, 1937.

14. Schiller, W., cited by Maxwell.[13]

one-half years after operation, her periods had continued regularly and the hirsutism had disappeared. This patient, according to Bergstrand,[15] later became pregnant.

Pathologic Report.—The specimen consisted of an irregularly round soft fluctuating growth, 8.5 by 8 by 6 cm., with a smooth lobulated surface, over one portion of which stretched a normal fallopian tube, while at another was attached a walnut-sized gray smooth spongy mass. On section the main portion of the specimen was composed of a lobulated growth, uniformly yellow and of brainlike consistency. The smaller nodule, which on section was grayish red, thinned out at its periphery to form a capsule about the main mass. On microscopic section the yellow tumor was composed largely of either round or polyhedral cells, measuring 30 to 35 microns, with distinct outlines and filled with fat and a finely granular cytoplasm. Other cells were present in which the granular cytoplasm was more abundant, stained darker and contained no vacuoles of fat. The supporting stroma consisted of a small amount of connective tissue accompanying the treelike course of the blood vessels. Tumor cells filled the spaces between the vascular branches. Regressive changes were noted, such as cells undergoing atrophy and replacement fibrosis. The walnut-sized mass consisted of ovarian tissue.

Bingel's[11] Case.—A 47 year old farmer's wife, who had married at 22, had given birth to 4 children. After the last pregnancy, at 29, her menstrual periods became irregular and remained so for five years, after which they stopped completely. At this time she suffered from headaches, the hair of the scalp fell out and she put on weight. Further, a beard and moustache appeared, so that at the age of 37 she had to shave daily. The voice changed, and she became cyanotic. Six years later polydipsia developed, the patient drinking 3 or 4 quarts (2,840 to 3,785 cc.) a day. Her physical appearance at this time was masculine. The hair on the head was thin, while that over the entire body was plentiful, particularly on the chest and abdomen. She had a strong bony framework, with well developed muscles. There was abdominal obesity. A hard mass the size of a grapefruit was felt in the lower part of the abdomen. Laboratory tests showed sugar in the urine, a red blood cell count of 8,900,000 and 130 per cent hemoglobin.

She was operated on on Sept. 19, 1919, the uterus and both tubes and ovaries being removed.

Pathologic Report.—An intramural fibromyoma the size of a grapefruit was present in the uterus. Whereas the left ovary appeared sclerotic, the right measured 9 by 9 by 4 cm. Section exposed a solid orange colored tumor surrounded by a capsule 3 to 4 mm. thick.

On microscopic examination the tumor was seen to be composed of irregularly shaped cells with large vesicular nuclei containing distinct nucleoli. Cytoplasm was abundant, granular and eosinophilic. The cells were arranged in irregular groups and strands similar to those in corpus luteum. The stroma was scant. No fat was demonstrated in the tumor cells. The author suggested the name lutein cell tumor. The left ovary was sclerotic.

She was followed for three years after operation, by the end of which time she had completely regained her feminine habitus. The hair on the scalp had grown back, and that about the chest, neck and shoulders had disappeared. She still had to shave twice a week, however. The red blood cell count was 5,600,000.

Sellheim's[10] *Case.*—The patient was a 49 year old woman who had been pregnant three times, one pregnancy resulting in miscarriage. Her menstrual

15. Bergstrand, H.: Ueber die Natur der virilisierenden Ovarialtumoren, Acta path. et microbiol. Scandinav., 1933, supp. 16, pp. 31-46.

periods began when she was 13 and ended abruptly at 43, the latter event having been associated with a gradual change of habitus to a coarse, masculine type. A heavy growth of hair appeared on the face and covered the entire body. At the same time the hair of the scalp began to fall out, the voice deepened and the larynx protruded.

Physical examination showed that the body was small, obese and coarse. She had a masculine face covered with beard and moustache. A dense growth of hair was present on the face, chest, abdomen, limbs and shoulders. The breasts were fatty, flat and pendulous. There was a penis-like clitoris, 4 cm. long by 1.5 cm. thick. A hard nodular mass filled the pelvis.

The operative procedure consisted in removing a large fibromyomatous uterus, together with both tubes and ovaries. The right ovary was small and sclerotic and the left of normal size. From the surface of the latter there protruded a chestnut-sized mass with a smooth surface.

Three weeks after the operation the beard grew lighter, the clitoris smaller and the voice softer. In ten months the clitoris was of normal size. At the end of a year all signs of masculinity had disappeared.

Pathologic Report.—Immediately after removal the tumor appeared grayish red. Microscopically it was composed almost uniformly of one type of polygonal cell, measuring 7 to 16 microns, with a distinct outline and filled with an abundance of granular cytoplasm that was free of fat and glycogen. The nuclei were round or oval, measured 6 by 9 microns and had prominent nucleoli. Scattered here and there was an occasional cell, almost twice the usual size, with the same type of cytoplasm and nucleus. A vascularized connective tissue stroma radiated in from the capsule to divide the growth into cellular masses of different sizes. Various opinions were offered as to the nature of the growth. Several physicians, Berbingler, Marchand and Lubarsch, leaned toward a diagnosis of hypernephroma. Mathias suggested, in addition, corpus luteum tumor. Regardless of its nature, he stated that it belonged to the same class as those in the case of Bovin and that of Bingel.

Case of Cosacesco and His Associates.[4]—A 34 year old woman complained of amenorrhea and masculinization of seven and five years' duration, respectively. Before this she had been perfectly normal. She had a lean masculine habitus. A dense growth of hair covered the face, chest, abdomen and extremities. In contrast, the frontal and parietal portions of the scalp were bald. The clitoris was large and the voice deep. *Per vaginam* an enlarged left ovary could be felt. Its removal initiated a dramatic reversal of symptoms. The menstrual flow appeared in thirty-two days and recurred regularly thereafter. Gradually her features and figure softened and the hirsutism disappeared, so that in two years she again appeared completely feminine.

Pathologic Report.—The ovary was round, 5 cm. in diameter and of cystic consistency. Section showed it to be a solid yellow nodule, encapsulated by a thin, firm fibrous coat, which microscopically was seen to be thinned ovary. The tumor was composed of cells of uniform size, filled with large quantities of lipoid, and was richly vascular. From the fibrous capsule, bands of fibrous tissue ramified through the growth, dividing it into small cellular nests.

Novak and Wallis' Case.[9]—The patient was normal until 30 years of age, when amenorrhea developed; this was followed in a few months by headaches, deepening of the voice, a change to the masculine habitus and the development of hirsutism, with a beard which required daily shaving. Physical examination showed her to be muscular, with a male build and hair on the face, chest, abdomen

and extremities. The clitoris was large. She had a deep voice. The sugar content of the blood during fasting was 150 mg. per hundred cubic centimeters. The red blood cell count was high, 6,600,000. The systolic blood pressure was 145.

At operation fluid was present in the abdomen, and the uterus and tubes were normal. Whereas the left ovary was small, the right was large, the size of a grapefruit.

Pathologic Report.—The specimen weighed 390 Gm. and measured 13.5 by 8 by 5 cm. Section showed one half to be composed of orange-colored tumor, with a gray, fibrous center. Independent but closely adjacent was a second nodule of similar nature. The remainder consisted of a grayish tissue—some portions compact and others more spongy because of contained blood vessels. Microscopically the nodules were composed of large, irregular polygonal cells, with a foamy cytoplasm rich in fat. The nuclei were large and in general vesicular. In the authors' opinion the tumor was of lutein cell origin, though they were not sure that it was not of adrenal origin.

One month after operation the periods returned and recurred regularly. Her habitus and voice gradually became softer, until at the end of two years she was completely femininized. The clitoris had become much smaller. Only the facial hairs were slightly heavier than normal, necessitating the use of a depilatory. The red blood cell count fell to 5,300,000 and the systolic blood pressure, from 145 preoperatively to 100 five months later. The blood sugar during fasting postoperatively was 115 mg. per hundred cubic centimeters. Determinations before operation showed no estrogen; after operation 200 mouse units was present.

Saphir and Parker's [12] Case.—The patient was a 15 year old girl with amenorrhea (for one year), hirsutism, obesity and deepening of the voice.

Physical examination showed obesity, confined to the trunk and face, and hypertrichosis of the cheeks, lips, chin, abdomen and chest. The mammae and clitoris were small, and the blood pressure was 110 to 130 systolic and 70 diastolic. Hormonal studies of the urine revealed an increase in estrogen and a decrease in the gonadotropic principle.

At operation the right ovary was seen to be slightly larger than its fellow. The right one was removed. Histologic examination showed a small, circumscribed nest of cells, with clear, vacuolated or finely granular eosinophilic cytoplasm. Both the cellular and the nuclear membranes were well defined. The authors felt that the nest of cells represented aberrant adrenal tissue.

Four days after operation a menstrual period occurred, and menstruation continued regularly for ten months (up to the date of the report). There was a slight loss of weight, but scarcely any change in the hypertrichosis. No vaginal cornification of the castrated mouse was obtained, even after an injection of 6 cc. of urine within one hundred hours.

Maxwell's [13] Case.—The patient was a 62 year old woman with an uneventful endocrine history except for sterility. Five years after the menopause hirsutism developed, so that she had to shave daily.

On physical examination she presented a slender, muscular, masculine habitus. The hair covering the scalp was short and sparse, whereas that covering the face, chest, back, abdomen and limbs was luxuriant. The voice was deep and the clitoris enlarged. The blood pressure was 200 systolic and 100 diastolic. There were 6,100,000 red blood cells and 16 Gm. of hemoglobin. The dextrose tolerance curve was abnormal, of diabetic type. Gonadotropic substances were absent from

the blood and urine. Estrogen was absent from the blood but present in the urine, up to 40 mouse units being excreted in twenty-four hours.

Both tubes and ovaries and the uterus were removed. The uterus contained many intramural fibroids. The right ovary was small and sclerotic. The left ovary was oval, measuring 4 by 2.5 by 1.5 cm.

Four months after operation the facial and bodily hirsutism had markedly decreased; the voice was softer, but the size of the clitoris had not diminished. A year later the breasts were larger and the figure had become more feminine. Hair had reappeared on the bald spots on the head and had practically disappeared over the body. She occasionally used a depilatory.

Dr. Maxwell sent us a slide containing a section from the left ovary, the description of which follows:

From the microscopic appearance of the slide the tumor must have been about the size of a pea. It occupied the medulla of the ovary and invaded slightly the cortex which encapsulated it. The tumor itself was composed of one type of cell, forming a diffuse, compact, richly cellular mass with no particular structure. The cells were slightly irregular in shape and size, averaging about 16 microns in diameter. A distinct cellular membrane was not visible. The cytoplasm was abundant, granular and eosinophilic. No clear cells were seen, so there was no suggestion of fat. Many cells contained coarse, brown granules. The nuclei were relatively large, round and oval, with granular chromatin material. In an occasional cell the nucleus was particularly large (up to 14 microns in diameter). Within the area occupied by the tumor cells were many blood vessels of varying size. In addition, there were many collapsed capillaries. The stroma was scant.

Summary of Clinical Findings (table 1).—The ages at which the patients came under observation ranged from 15 to 62 years, one to thirteen years after the onset of symptoms. In the youngest patient the onset occurred at 14 years, two years after the first menstrual period; in the oldest, at 50 years, five years after the menopause, and in others, at 21, 27, 30, 34 and 43 years. Neither sterility nor unusual fecundity appeared related to the syndrome, since 4 patients had from 1 to 4 children and only 1 was definitely sterile. When recorded, the establishment of menstruation, its continuance and its regular recurrence were normal. In every case except that (postmenopausal) reported by Maxwell, amenorrhea ushered in the syndrome. In 3 instances there was no antecedent disorder. In the others there were abnormalities such as irregular or diminished flow. Once established the amenorrhea was absolute, except in Sellheim's case, in which after eight years the patient suddenly began to bleed again. It is interesting that at about the time when there should have been a menstrual period one patient had recurrent headaches, mucous discharge and pain in the back.

After amenorrhea a train of other changes ensued, transforming the wholly feminine person into one with masculine characteristics, such as hirsutism, a deep voice, hypertrophy of the clitoris and a male habitus. These changes occurred either simultaneously with amenorrhea or developed at varying intervals, from six months to two years, except in Maxwell's patient, in whom they occurred five years after the meno-

pause. Once initiated, the transformation proceeded inexorably until fully established within a year.

The most conspicuous symptom was hirsutism. This was characterized by a generalized increase of dense, coarse hair that would have done justice to any man. It grew over the cheeks, chin, neck and lips at a rate necessitating daily shaving. Further, it covered the chest, back, limbs and abdomen in true male fashion. In contrast to the hypertrichosis of the body, in 4 cases the hair of the scalp proceeded to fall out, producing bald spots. All patients had changes in voice. In 3 the voice was described as deep or hoarse, while in the others it was still suffi-

TABLE 1.—*Clinical Features of Cases Reported in the Literature* *

Case †	1	2	3	4	5	6	7
Age	34	28	49	15	47	32	62
Number of children	0	2	2	0	4	0	0
Age at onset of menstruation	—	—	18	12	—	12	16
Age at onset of amenorrhea	27	21	43	14	34	30	45
Age at onset of hirsutism	29	22	43	14	34	30	50
Loss of hair on scalp	Yes	—	Yes	No	Yes	Yes	Yes
Enlargement of clitoris	3-4 cm.	—	4×1.5 cm.	No	—	3.5 cm.	Yes
Change in voice	Yes	—	Yes	Yes	Yes	Yes	Yes
Atrophy of breasts	Yes	No	Yes	Yes	—	Yes	Yes
Thyroid enlargement	—	—	—	—	Yes	Right lobe	Right lobe
Habitus	Male	—	Male	Female	Male	Male	Male
Headache	—	—	—	—	Yes	Yes	—
Loss of libido	Yes	—	Yes	—	No	Yes	—
Cyanosis	No	Yes	Yes	No	Yes	No	No
Weight	Thin	—	Obese	Obese	200 lb. (90.7 Kg.)	159 lb. (72 Kg.)	Thin
Erythrocyte count	—	—	—	—	8,900,000	6,600,000	6,100,000
Hemoglobin	..	..	..	..	130%	110%	
Blood sugar	—	—	—	Normal	Increase	150	‡
Blood pressure	—	—	—	110/70	120	145	220/100

* Dashes indicate that no data were given.

† The numbers in this and subsequent tables refer to the reports of the following authors: (1) Cosacesco and associates, (2) Bovin, (3) Sellheim, (4) Saphir and Parker, (5) Bingel, (6) Novak and Wallis and (7) Maxwell.

‡ The dextrose tolerance test showed a curve characteristic of diabetes.

ciently high pitched to be considered feminine. The laryngeal cords were found enlarged in 2 instances and normal in 1; in the other cases there was no examination. Further, in 1 case the larynx protruded externally, producing a so-called Adam's apple. To complete the change, a male habitus developed in 5 instances, with some of the following features: increase in musculature, widening of the shoulders, loss of female panniculus, development of veins on the arms, coarsening of the skin, angularity and coarse features and leanness. The youngest patient retained her female figure but became obese, chiefly over the trunk, neck and face. In 2 cases the habitus was not described. Definite changes were noted in the breasts in every instance. In some cases they diminished in size, becoming flat and atrophic; in others they became

flabby and pendulous. When the clitoris enlarged (in 4 cases) it did so to a marked degree, becoming in some instances penile in appearance. In 1 case there was no change, and in 2 its condition was not mentioned. Another interesting feature was the development in 3 patients of a livid complexion. This had its basis in polycythemia. Concerning the thyroid, of 4 cases in which its size was noted, it was normal in 1, in another the right lobe was enlarged, in a third the right lobe contained a calcific mass (the patient had symptoms of hyperthyroidism) and in the last there was general enlargement. Definite hypertension was present in 1 case.

Laboratory data in most instances were meager. The abnormal findings can be summarized as follows: In 1 case there was glycosuria; in 3, polycythemia. In 1 the dextrose tolerance curve was of the diabetic

TABLE 2.—*Changes Following Removal of Tumor*

Cases	1	2	3	4	5	6	7
Return of periods	32 days	2½ mo.	Uterus removed	4 days	Uterus removed	28 days	Uterus removed
Diminution of hirsutism	Normal 2 yr.	Normal 9 mo.	Normal 1 yr.	No	Some; still shaved after 3 yr.	Marked; still had to use depilatory	Marked
Return of scalp to normal	Yes	—	Yes	—	Yes	Yes	Yes
Return of voice to normal	Yes	—	Yes	—	Yes	Yes	Softer
Shrinking of clitoris	No mention	—	Yes	—	—	Yes	Same after 4 mo.
Return of female habitus	2 yr.	—	1 yr.	—	Yes	Yes	Yes
Weight	—	—	—	Slight loss	35 lb. lost (16 Kg.)	—	Gain
Erythrocyte count	—	—	—	—	5,600,000	5,300,000	—

type. In 1 the sugar content of the blood was 150 mg. per hundred cubic centimeters. For the patient who had glycosuria no values for blood sugar were reported. This patient was considered diabetic. In another case the chemical composition of the blood was reported as normal, but no values for sugar were given. Hormone studies, when done, showed absence of both the follicle-stimulating and the luteinizing gonadotropic substance. Estrogen was absent in Novak's case and consisted of 5,000 mouse units per liter in Saphir and Parker's and of 40 mouse units in twenty-four hours in Maxwell's.

As dramatic as the development of masculinity was the development of female traits following operative removal of the ovarian tumor (table 2). In the 4 instances in which hysterectomy was performed the first change to occur was the prompt return of a normal menstrual period; at the end of four days in 1 case, twenty-eight days in another, and thirty-two and seventy days, in the others. Once established, the

periods recurred regularly throughout the period of observation. Softening of the voice followed in every instance promptly, the change being noted as early as one and a half months. Where the male habitus had been established, the change in bodily configuration proceeded toward that of the female, so that in periods varying from one to three years the transformation was complete. With 2 exceptions hirsutism was likewise affected. The hair began to fall out, could be plucked more easily, became finer and grew more slowly. These changes were noted as early as three weeks after operation. In some instances the hair returned to the original status. In others at the end of the period of observation it was markedly diminished and softer, but still heavy enough to necessitate the use of depilatories or shaving at long intervals. In cases in which partial baldness had developed hair began to grow on the head again, until once more the distribution was feminine. One patient who was obese lost weight; another who had been lean gained. With 1 exception the clitoris diminished in size in all cases, even as early as three and a half weeks after operation. In 1 case (that of Novak and Wallis) the systolic blood pressure dropped from 145 mm. before operation to 100 mm. five months after operation. Also interesting was the diminution in number of red blood cells in cases of polycythemia. The most marked change was in Bingel's case, in which the count fell from 8,900,000, with 130 per cent hemoglobin, before operation to 5,500,000, with 100 per cent hemoglobin, one month after operation. The sugar content of the blood in Novak's case fell from 150 mg. per hundred cubic centimeters (fasting specimen) before operation to 115 mg. afterward. Hormone studies in the case of Saphir and Parker showed that the estrogen content, at first high, fell to low values. In Maxwell's case it reached zero. In the case reported by Novak and Wallis there were no gonadotropic or estrogenic substances.

Pathologic Data (table 3).—The tumor was in the right ovary in 4 cases and in the left in 3 cases. In 6 cases it was grossly evident, the largest tumor measuring 13.5 by 8 by 5 cm. The average tumor was equivalent in size to a chestnut. One growth was evident only microscopically (Saphir and Parker's case). Another (Maxwell's case), judging from its size in the histologic preparation, must have been about 1 cm. in diameter. All the tumors were solid, felt cystic or rubbery and were oval and yellowish orange except one, which was reddish gray. Every one was completely or partially encapsulated, usually by thinned-out ovarian cortex. On section the tumor usually was lobulated by fibrous septums radiating in from the capsule. In 1 case the central portion contained an irregular patch of gray fibrous tissue. In some cases the growth occupied the medullary portion of the ovary. The tumor reported by Bovin was parovarian. In Sellheim's report the location was not clearly described.

Microscopic Features of the Tumors.—In all specimens the tumor tissue was richly cellular, the cells forming no particular pattern. They filled in the spaces of a network formed by capillaries branching out from scattered large vessels. Fibrous stroma was scant following these vessels. In 2 cases stains for reticulum were used and revealed fine, silver fibrils encircling single cells or small groups of cells. In 1 instance the stroma was more richly fibrous and was described as a network formed by branching septums radiating in from the capsule. In the case reported by Saphir and Parker the growth consisted of a small nest of cells. The cells composing the tumor, in general, were uniform in type, relatively large and polyhedral; they had distinct outlines in 5 cases. The cytoplasm was granular, eosinophilic and variable in amount. Many of the cells appeared clear owing to the scant amount of cytoplasm dispersed by the fat content.

TABLE 3.—*Pathologic Data in Cases of Ovarian Tumor*

Case	Condition of Uterus	Description of Tumor				Condition of Opposite Ovary
		Location	Size, Cm.	Color	Solid	
1	Normal	Left	5	Yellow	Yes	—
2	Normal	Left	8.5×8×6	Orange	Yes	Small, sclerotic
3	Large fibroid	Left	Approx. 4	Gray-red	Yes	Small, sclerotic
4	Normal	Right	Microscopic	—	—	Normal
5	Large fibroid	Right	9 × 9 × 4	Orange	Yes	Small, sclerotic
6	Normal	Right	13.5 × 8 × 5	Orange	Yes	Small
7	Many fibroids	Right	Approx. 1	—	Yes	Sclerotic

In 4 cases the clear cells predominated. In no instance in which chromaffin granules or glycogen were looked for were they demonstrated. The nuclei were either oval or round; some were rich in chromatin, giving the body a dark appearance; others were vesicular. Nucleoli were observed in all. In addition to clear cells, others were present in which the cytoplasm was more abundant and fat was absent.

In the 3 remaining cases the tumor consisted, predominantly in 1 and exclusively in the other 2, of a densely eosinophilic cytoplasm. Fat was absent in 3. In 1 case (Maxwell) coarse brown granules were present in the cytoplasm. Degenerative phenomena were described in 5 cases. In 2 these consisted of frank necrosis. In the others there was disappearance of the tumor cells by atrophy and by fibrous replacement. In those cases in which ovarian tissue was present primordial and developing follicles were noted, but no corpus luteum other than dense hyalinized fibrous remains. In Maxwell's case even these were absent.

In all cases the tumor was benign—at least no recurrence took place during the period of observation. In 4 cases there was fibromyoma of the

uterus. In 1 the uterus was smaller than normal. In 3 there was fluid in the abdominal cavity, and in 2 there were adhesions of the tumor to adjacent structures. The opposite ovary, free of tumor, was described either as of normal size or as small and atrophied.

REPORT OF CASES

CASE 1.—A woman of Spanish parentage, born in France, came under the observation of the outpatient service of St. Vincent's Hospital in February 1935, when she was 23 years of age. She had not menstruated since May 25, 1934, and believed herself pregnant. In addition, she complained of severe headaches in the frontal region. Her menstrual periods had begun at 14 years and were regular, occurring every twenty-eight days and lasting three days. She married at 17 and had a baby at 18, whom she nursed for more than twelve months. There were no other pregnancies, though contraception was not practiced. For more than one year prior to the onset of amenorrhea she had noticed a marked overgrowth of hair on the face, chest, back and extremities.

Examination showed her to be short and obese—61 inches (155 cm.) tall and weighing 177 pounds (80.3 Kg.). Three years before she had weighed 100 pounds (45.4 Kg.). The obesity was chiefly of the trunk, neck and face, being less marked in the extremities. No objective evidence of pregnancy was found. The breasts were not large; no secretion was present. There was no enlargement of the abdomen. Vaginal examination disclosed a soft cervix and a small uterus in good position with no adnexal abnormality. Marked hirsutism was noted. The thyroid was palpable though not enlarged. The blood pressure was 110 systolic and 70 diastolic.

She attended the outpatient clinic for one month and then was not heard of again until May 25, 1937, when she was brought to the hospital because of severe renal colic, chills, fever and vomiting. After a few days the acute symptoms subsided, and attention was focused on the remarkable hirsutism displayed. Since her last visit to the outpatient clinic she had begun to shave, first the chest, in 1936, and later the face. Whereas in the beginning she shaved the face once a week, soon it was necessary to do so daily. The amenorrhea continued. The voice had become deeper and headaches persisted, recurring at monthly intervals. She had become nervous, timid and depressed about her condition. There had been no change in libido.

Physical examination on May 25 showed the blood pressure to be 90 systolic and 60 diastolic. The patient was moderately obese, weighing 161 pounds (73 Kg.), with female habitus. The voice was slightly husky but still feminine. There was pronounced hypertrichosis of the entire body, the hair being heavy, black, coarse and of definitely male distribution, with a decided beard and pudendal excess, extending above the umbilicus. The arms and legs were heavily covered, as were the dorsal surfaces of the fingers and toes. The eyes were prominent. Her bodily contour was decided abnormal, with large flabby pendulous breasts; flabby fat cheeks; a double chin, and a definitely obese waistline and pelvic girdle. There was marked hypertrophy of the clitoris, with some diminution in the dimensions of the vaginal tube, the cervix and the fundus uteri. When the patient was conscious, it was impossible to demonstrate any adnexal abnormality. During anesthesia, however, the right ovary was felt to be enlarged.

Urologic study revealed a calculus in the left kidney, with infected hydronephrosis. Roentgen examination of the skull, sella turcica and long bones revealed

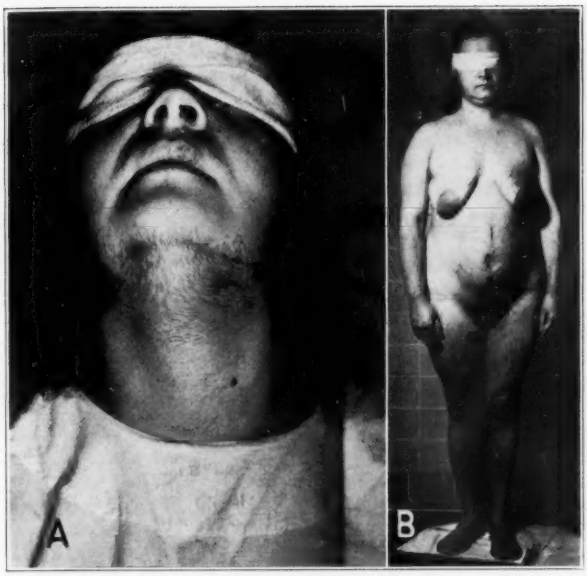

Fig. 1 (case 1).—*A*, facial hirsutism before operation, two days' growth. *B*, female habitus and generalized hirsutism on face, chest, abdomen and limbs. Breasts are flat and pendulous and the trunk, neck and face obese.

Fig. 2 (case 1).—Hypertrophy of the clitoris.

no unusual changes other than what seemed like exostoses on the inner plate of the frontal bone. Aerograms of both adrenal regions failed to confirm the presence of any abnormality.

With subsidence of the renal disability, laparotomy was performed on June 16. Palpation and inspection of the pelvic viscera revealed that the uterus and tubes were normal; the left ovary seemed smaller than normal and so sclerotic that it could no longer function. Nothing suggestive of recent or old corpus luteum could be demonstrated in either ovary. The right ovary was enlarged, firmly resilient and of regular outline and had an unusually white tunica. It was removed after careful palpation of both renal and adrenal regions had failed to demonstrate any adrenal tumor. The patient made an uneventful recovery and was discharged on June 30.

Laboratory Data.—The urine on entry contained albumin and numerous red and white blood cells. The blood count at this time showed 30,000 leukocytes, with 95 per cent polymorphonuclears and 5 per cent lymphocytes, 5,000,000 erythrocytes and 15 Gm. of hemoglobin (Sahli). On discharge the white cell count had fallen to 8,480, with 66 per cent polymorphonuclear leukocytes and 34 per cent lymphocytes; the red cell count was 5,150,000. The urine became free from red cells, and the number of white cells diminished.

Chemical analysis of the blood showed 111 mg. of sugar, 36 mg. of nonprotein nitrogen, 432 mg. of chlorides, 144 mg. of cholesterol, 10.4 mg. of calcium, 3 mg. of phosphorus and 293 mg. of sodium per hundred cubic centimeters. The carbon dioxide content was 47 cc. per hundred cubic centimeters. The dextrose tolerance test showed 72 mg. of sugar per hundred cubic centimeters during fasting, 124 mg. half an hour after ingestion of 100 Gm. of dextrose, 202 mg. after one hour, 222 mg. after one and one-half hours, 211 mg. after two hours, 158 mg. after three hours and 60 mg. after four hours.

Tests for the follicle stimulating gonadotropic substance gave negative results. The estrogen content of the urine[16] was 3.3 rat units per liter. Two specimens assayed for androgenic substance[17] showed 17.3 and 15.7 international units.

Postoperative Course.—On July 17 the patient had a normal menstrual period. By August 3 the voice had become higher pitched and the clitoris smaller; the hair on the body had begun to fall out and grow more slowly.

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16. Estrogen was extracted from a twenty-four hour specimen of urine by a method outlined by B. Harrow and C. P. Sherwin (The Chemistry of the Hormones, Baltimore, Williams & Wilkins Company, 1934, p. 167). The extract was taken up in oil and given to Dr. H. C. Taylor, of the New York University Medical College, Department of Gynecology, who assayed it by injecting it into rats.

17. Two twenty-four hour samples of urine were extracted after the method of Funk and Harrow (Harrow, B., and Sherwin, C. P.: The Chemistry of the Hormones, Baltimore, Williams & Wilkins Company, 1934, p. 157). These were taken up in 25 cc. of oil and assayed by Dr. W. K. Cuyler, of the Cleveland Clinic Foundation Hospital. Each sample was injected into a group of birds, 1 cc. per day being given to each bird. The experiment was controlled by means of a group of birds which received 1 international unit of androsterone per bird per day, after the manner of T. F. Gallagher and F. C. Koch (Quantitative Assay for Testicular Hormone by Comb-Growth Reaction, J. Pharmacol. & Exper. Therap. **55**:97, 1935). Dr. Cuyler criticized the method we adopted for extracting the urine, on the ground that the yield by this method is only about 60 per cent.

On October 12 she was readmitted to the hospital, and a calculus was removed from the pelvis of the right kidney. Her convalescence was uneventful, and she was discharged on November 5. The blood pressure was 78 systolic and 14 diastolic. The dextrose tolerance test at this time showed 74 mg. of sugar per hundred cubic centimeters during fasting, 191 mg. one hour after ingestion of dextrose, 140 mg. after two hours, and 25 mg. after three hours (she felt dizzy at this point). The basal metabolic rate was + 25 per cent and on repetition of the test + 10 per cent.

She was seen again on November 3. She appeared happy, was slimmer and weighed 141 pounds (64 Kg.). The hairs on her body were softer, less dense and lighter. She now shaved every two weeks. The periods were recurring regularly. The headaches had disappeared entirely.

On December 4 she reported that she had menstruated normally in November. She had allowed the facial hair to grow for three weeks so that a photograph could be taken. A definite beard was present, but it was much lighter and scantier than what grew in two days before operation.

Fig. 3 (case 1).—Facial hirsutism six months after operation, three weeks' growth.

On Feb. 14, 1938, menstruation was reported as normal. A dextrose tolerance test by the Rose-Exton method showed 80 mg. per hundred cubic centimeters during fasting, 143 mg. half an hour after ingestion of dextrose and 160 mg. after one hour. She was shaving once every two weeks.

In April menstruation was still normal. The patient weighed 140 pounds (63.5 Kg.). The hair on the chest had disappeared. There was still a slightly greater amount than normal on the limbs. She continued to shave on an average of every two weeks. The double chin was almost gone.

Pathologic Report.[18]—The specimen was an oval, resilient mass weighing 22 Gm. unfixed and measuring 4.5 by 1.5 by 1.5 cm. The outer surface was smooth, even, shiny and pearly gray.

18. The technic of study was as follows: One half of the specimen was saved for display in the museum; the other was cut into many blocks. These were fixed separately in a 10 per cent dilution of solution of formaldehyde U. S. P., and

(Footnote continued on next page)

Section exposed a solid, sharply demarcated, spherical nodule, 3 by 2.5 cm., composed almost entirely of orange-colored tissue, except for the central portion, where there were small, irregular, gray areas. Fine strands of the same gray tissue divided the orange mass into small lobules. The nodule lay eccentrically in a tough, fiberlike capsule, which at one pole was only 1 mm. thick and tough. At the opposite pole, the region of the hilus of the ovary, the capsule was thicker (5 cm.) and more spongy, owing to the presence of many small, thick-walled vessels.

Microscopic Examination.—The nodule was composed of a uniform type of cell laid down in continuous sheets between the numerous branches of the vascular

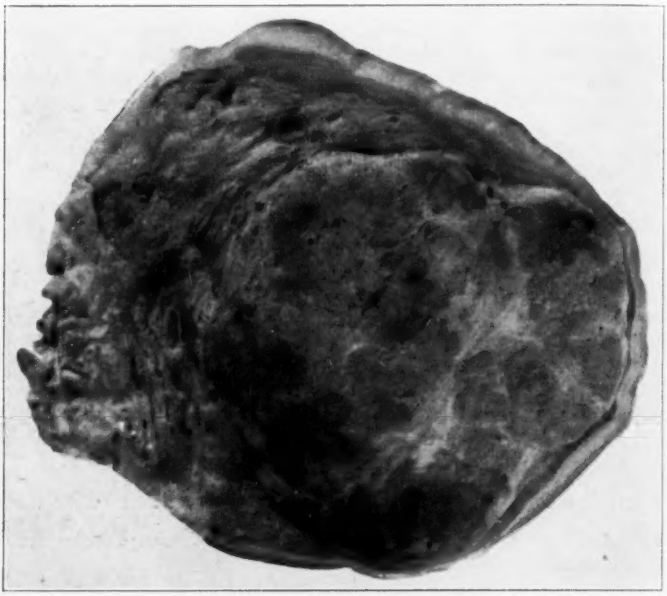

Fig. 4 (case 1).—Solid orange-colored nodule encapsulated by thinned-out ovary.

in Zenker, Bouin, Regaud, Mann and Bensely solutions. They were embedded in paraffin and the sections stained with the following solutions: hematoxylin and eosin, the Weigert stain for elastic tissue, the Masson trichrome stain and the Foot and Foot stain for reticulum. Vines' stain (Broster, L. R., and Vines, A. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Co., Ltd., 1933) was used to demonstrate the possible presence of fuchsinophilic granules. The fat content was studied with scarlet red and osmic acid. Blocks fixed in absolute alcohol were embedded in pyroxylin and stained with Best's carmine stain in order to demonstrate the presence of glycogen. Granules of chromaffin were looked for in material fixed in Regaud's solution.

tree. The larger vessels, of which there were many, were surrounded by moderate amounts of connective tissue, which diminished as the twigs became smaller. Distributed about the capillaries and surrounding cells individually and in small groups was fine reticulum demonstrated with silver. No elastic tissue was seen other than that forming part of the walls of the blood vessels.

The tumor cells varied slightly in size, from about 10 to 16 microns. The membranes stood out distinctly, outlining their oval, round, irregular and polyhedral shapes. The cytoplasm was granular, eosinophilic and for the most part scant, so that in the hematoxylin and eosin preparation the cells looked clear. This was due to fat being dissolved out of the paraffin-embedded sections. Other substances, such as glycogen, chromaffin and fuchsinophilic granules, were absent. In material fixed in Bouin's solution, the stained granules were especially

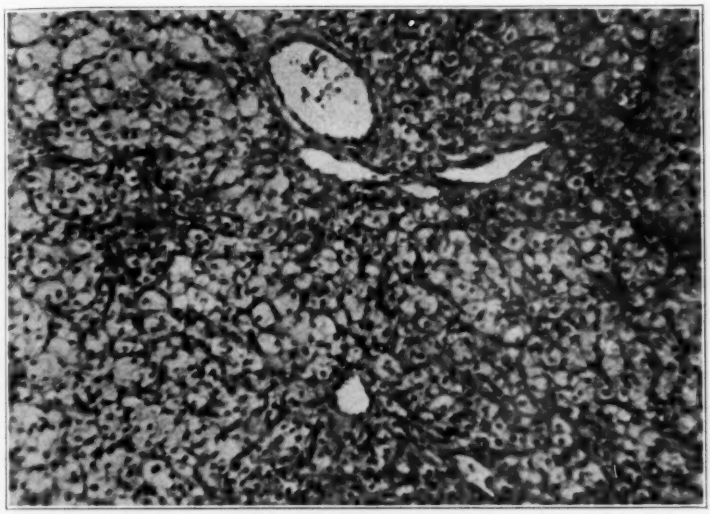

Fig. 5.—Photomicrograph; low power; hematoxylin and eosin stain, showing large polyhedral cells, clear cytoplasm and distinct cellular outlines.

fine and so arranged as to give the cell a foamy appearance. In material fixed in other solutions the granules were coarser and clumped about the nucleus. The nucleus was seen to best advantage in tissue fixed in Mann's solution. It was of moderate size and oval or round—variously located in the cell—and had a thick, sharp nuclear membrane, a nucleolus and a small amount of chromatin. Less common were irregular masses of similar but smaller cells in which fat was scant or absent. The cytoplasm of these cells appeared more eosinophilic, since it was less spread apart by lipoid content. Also present were groups of small, shrunken cells entangled in thickened hyalinized reticulum. In some places there were areas composed almost entirely of the latter material. This change, evidently a degenerative one, was most marked in the central gray portion of the nodule.

The capsule was seen to consist of thinned cortex of ovary. In it there were primordial follicles, small developing follicles and compact hyalinized fibrotic rem-

nants of old corpora lutea. Whatever tissue of the underlying medulla remained unoccupied by tumor was thinned out about its periphery.

Curettage produced a small bit of tissue, which disclosed a thin layer of endometrium containing occasional small glands lined with tall epithelial cells. The nucleus lay at the base of each cell. The stroma cells were small, with scarcely any cytoplasm.

CASE 2.[19]—The patient was first observed in 1923, at the age of 25. She had been married one year and had not become pregnant. Physical examination disclosed an enlarged uterus. At operation the tubes and ovaries were normal, but the uterus, which was smooth and symmetrically enlarged by a fibroid, was removed.

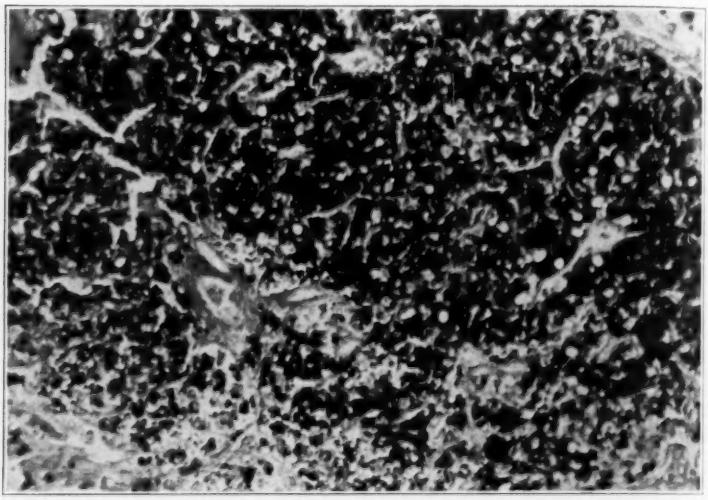

Fig. 6.—Section stained with osmic acid, showing heavy reaction.

During a routine examination five years later an abdominal tumor and fluid were discovered. She had no complaints other than that her voice had become deeper soon after the operation and, further, that the amount of hair over her body had progressively increased, so that she found it necessary to shave. On examination the blood pressure was 130 systolic and 70 diastolic and the pulse rate 112. The heart and lungs were normal. The abdomen was soft. Fluid was evident, as was a hard, nontender mass in the right lower quadrant. There was an abnormal growth of hair of male distribution over the abdomen, legs, arms and face. The habitus was female.

Vaginal examination revealed a normal clitoris and a small, healthy introitus with a freely movable cervical stump. The cul-de-sac was filled with a hard, fixed, irregular tumor, continuous with the abdominal mass. The left broad ligament was thickened. On this side a small growth was likewise palpated.

19. This case is included with the permission of Dr. William S. Smith, of the Brooklyn Hospital.

Laboratory Data.—A blood count showed 4,500,000 erythrocytes, 83 per cent hemoglobin and 11,200 leukocytes, with 80 per cent polymorphonuclears, 2 per cent eosinophils, 2 per cent monocytes and 16 per cent lymphocytes.

Operation.—On April 23, 1928, 2 quarts (1,893 cc.) of fluid was present in the peritoneal cavity. Both ovaries were occupied by solid growths. That on the right was lobulated. The one on the left was the size of a goose egg. Both were adherent to bowel and bladder. After the adhesions had been freed it was possible to remove the ovaries. Recovery was uneventful. Dr. James Denton, pathologist, reported the specimen as consisting of several irregularly shaped masses, each 3 or 4 cm. in diameter, having a deep yellow-orange color. The histologic diagnosis was bilateral ovarian luteoma.

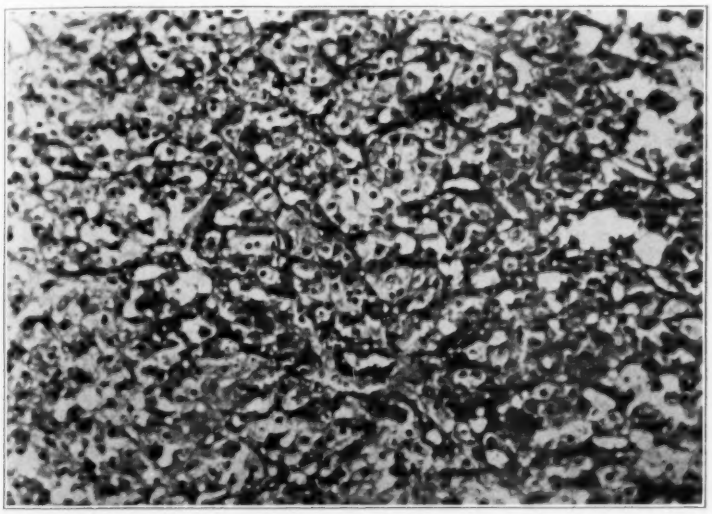

Fig. 7 (case 2).—Section stained with hematoxylin and eosin (low power), showing polyhedral shape, large size, distinct cellular outlines and clear cytoplasm.

Postoperative Course.—On discharge, on May 14, her general condition was excellent. The cervical stump was fixed and the vaginal vault indurated. On May 24 high voltage roentgen therapy was begun.

On July 24 the voice was not nearly so deep. The excess hair on the body was disappearing. Vaginal examination showed the cervix to be free and movable and the vaginal wall soft and pliable. The patient appeared and felt well.

She remained free from symptoms until October 1931, when her voice again began to deepen and the body hair started to grow to excess. Vaginal examination revealed a hard mass, the size of a marble, behind the cervix. In the belief that there was a recurrence, roentgen therapy was resumed.

On December 9 a hard walnut-sized nodule was discovered in the abdominal scar, and the pelvic tumor was noted to have increased in size.

On Jan. 8, 1932, she was operated on again. The intestine was infiltrated with tumor adherent to that present in the abdominal wall. In the pelvis, behind the

sacral promontory, was a mass, 7.5 by 5 cm. The growth was found to be inoperable. She recovered from operation; but in three months intestinal obstruction developed, and she reentered the Brooklyn Hospital in March. Intestinal anastomosis was performed. She grew worse and died on July 7.

It had been noted that her voice was deeper and that the amount of hair on the body had increased. No autopsy was done.

Microscopic Examination.—A biopsy specimen from the abdominal nodule showed identical structure with that of the original ovarian growth. The evidence definitely indicated tumor of the corpus luteum, though the question of carcinoma of an adrenal rest was raised. It was our privilege to examine a microscopic preparation of the original growth in the ovary, a description of which follows:

The tumor microscopically was composed of a uniform type of cell with a thick, distinct border. The cells were about 8 to 16 microns in breadth and polyhedral. The cytoplasm was granular and eosinophilic and in some cells abundant and in others scant, giving the cell in the latter instance a clear appearance. Though no stains for fat were employed, the appearance of the cytoplasm strongly suggested the presence of fat. No granules of pigment were evident. The nuclei were of moderate size. Chromatin was abundant and coarsely granular. Nucleoli were present. The tumor was traversed by many small blood vessels, from which radiated capillaries, forming a network in which the tumor cells lay in cords and sheets. Because the capillaries were collapsed, the first impression was that the tumor was composed of a solid sheet of cells. In one portion, equivalent to about one third of the section, there was complete necrosis of the tumor.

COMMENT

Our first case certainly was an instance of the condition under discussion, for clinical masculinity developed in a patient who previously had been completely feminine. Further, an orange-colored nodule composed of large clear fat-containing cells occupied the medulla of the right ovary. Lastly, the reversal of symptoms following removal of the right ovary established it as the sole and primary site of the growth. In the second case (Smith), though histologically an instance of the same condition, there were certain atypical features. The hysterectomy prevented the establishment of nonsurgical amenorrhea; the tumor was bilateral and malignant. Since in the other reported cases and in ours the growths were benign, the possibility of metastasis in Smith's case is suggested. In refutation, we have the established clinical fact that the symptoms receded after removal of the growth, only to reappear with recurrence of the growth.

Concerning the nature of the tumor, we are as much in the dark as were our predecessors. Various physicians who have studied slides made in our case (E. Novak, R. Meyer, W. Schiller and D. Symmers) have expressed the belief that the growth arose from an adrenal rest. Vines, who with Broster [20] made a special study of adrenal tissue in cases of the adrenogenital syndrome and who examined slides made in our

20. Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Co., Ltd., 1933.

case, stated emphatically that the growth was not of adrenal origin and suggested luteinic origin instead. Otto Saphir, who also studied a slide, came to the conclusion that the appearance was not similar to that in his case, which he felt was an instance of true adrenal rest, while ours was one of true tumor-luteoma or hypernephroid.

The facts in favor of the theory that the tumor arose from an adrenal rest were:

1. It was orange colored.

2. Its component cells resembled those of adrenal cortex.

3. Adrenal cortical tumors have produced similar syndromes (Bullock and Sequeira [21]).

4. Adrenal cortical tumors producing masculinization have been reported outside the adrenal gland (Kolodny [22]).

5. Adrenal rests have been described along the course followed by the ovary in its descent and within the ovary itself (Meyer [23]). The authenticity of a true adrenal rest in the ovary proper was contested by Glynn.[2]

6. The presence of a distinct cellular membrane has been offered as evidence favoring its adrenal origin by Schiller.[24] This argument, in our opinion can hardly be valid, since it is not unusual to see distinct outlines in cells which are fatty and clear. Examples are the cells of renal hypernephroma, lutein cells during regression of the corpus luteum, hepatic cells during so-called cytolytic degeneration and the cells of so-called corpus luteum tumor associated with femininity, which will be described later.

7. It is doubtful whether a cell as highly differentiated as a lutein cell can give rise to a tumor.

8. Further doubt is cast on the origin from corpus luteum when one considers that the function of the corpus luteum is to regulate the endometrium preparatory to nidation, a function far removed from the production of masculinization.

In favor of the tumor's luteinic origin authors have pointed to the following facts, some of them the same as in the preceding group:

1. The tumor is of yellow-orange color.

2. Its cells resemble those of corpus luteum. The cells of the latter, however, appear similar only when the corpus luteum regresses.

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21. Bullock, W., and Sequeira, J. A.: On the Relation of the Suprarenal Capsule to the Sexual Organs, Tr. Path. Soc. London **56**:189, 1905.

22. Kolodny, A.: Suprarenal Virilism in a Woman: Tumor of an Extrarenal Suprarenal Rest, J. A. M. A. **102**:925 (March 24) 1934.

23. Meyer, R.: Personal communication to the authors.

24. Schiller, W., in discussion on Rottino, A.: Ovarian Adenoma Associated with Masculinization, Arch. Path. **25**:928 (June) 1938.

3. The tumor in question inhibits full development of graafian follicles and ovulation, as does corpus luteum, thus leading to amenorrhea.

4. Bergstrand [15] cited the work of Steinach and Kun, who injected extract of corpus luteum into young spayed female guinea pigs and noted virilizing effects.

Meyer [25] countered by asking what virilizing symptoms in a female guinea pig were.

Inconclusive as the aforementioned arguments may be, they nevertheless indicate that an adrenal rest is a more probable source of origin than corpus luteum.

The subject of hypernephroid and luteoma is complicated further by another group of tumors also labeled luteoma. These are associated not with masculinization but rather with a clinical picture analogous to that produced by granulosa cell growths. The subject was reviewed in 1917 by Glynn,[2] who said that 14 tumors described as ovarian hypernephromas were analogous to 9 others described in the literature as lutein growths. Novak and TeLinde [26] questioned the nature of 5 of them and gave evidence that they were of other origin. Other contributions followed under different headings, such as *folliculome lipidique* (La Cene [27]); granulosa cell tumor (Plate;[28] Benda and Krause [29]) and luteoma or corpus luteum tumor (Wolf;[30] Wills and Romano;[31] Cutler [32]).

The clinical features described in the later reports were similar to those in the cases reviewed by Glynn, except that some of his patients were older—in the fifth, sixth and seventh decades—whereas in the later cases the patients were 21, 22, 23, 26 and 38 years of age. In no case were there symptoms of masculinization. The chief disorder was excessive and prolonged bleeding for two to six months, followed in 3 cases by amenorrhea. In 1 case the breasts enlarged, and in 2 a secretion could be expressed. In the 1 instance in which the endometrium was

25. Meyer, R.: Ueber die Natur der virilisierenden Ovarialtumoren, Ber. ü. d. ges. Gynäk. u. Geburtsh. **27**:113, 1934.

26. Novak, E., and TeLinde, R.: The Pathological Anatomy of the Corpus Luteum, Bull. Johns Hopkins Hosp. **34**:298, 1923.

27. La Cene, cited by Plate.[28]

28. Plate, W. P.: Eine seltene Form eines Granulosazelltumors des Ovariums, das sogenannten: "Folliculomelipidique," Arch. f. Gynäk. **153**:318, 1933.

29. Benda, R., and Krause, E. J.: Luteinisierter Granulosazeltumor mit Amenorrhea, Arch. f. Gynäk. **157**:400, 1934.

30. Wolf, S. A.: Luteoma, Am. J. Obst. & Gynec. **13**:575, 1927.

31. Wills, S. H., and Romano, S. A.: A Case of Luteoma, Am. J. Obst. & Gynec. **29**:845, 1935.

32. Cutler, O. I.: Corpus Luteum Tumor, Am. J. Obst. & Gynec. **30**:131, 1935.

studied it was hyperplastic. Removal of the tumor-bearing ovary resulted in reappearance of menstruation in the patients with amenorrhea and the establishment of normal bleeding in those with menorrhagia.

All but 1 of the tumors were unilateral. None was reported malignant. They were solid. In 1 tumor there were areas of degeneration causing formation of small cysts. Their size varied: 1 measured 15 by 10 by 5 cm. and another 3.5 by 4.5 by 6 cm. The growth occupied the central portion of the ovary, the cortex of which was stretched into a thin capsule around it. The one exception was that in the case of Benda and Krause. There was an almond-shaped, flattened ovary on the medial aspect of the tumor, from which it could be separated. The tumor was usually yellow, with scattered irregular areas of fibrous tissue. Grossly, therefore, the tumors resembled those of the so-called hypernephroid group.

Histologically they were very cellular. In two reports (Wills and Romano; Wolf) the cells were said to be arranged in alveoli of varying sizes surrounded by fibrous septums. The tumor cells were large, irregular and polyhedral, with distinct outlines and a granular eosinophilic cytoplasm which for the most part was scant. The nuclei were flattened out against the cellular membrane by contents strongly suggesting fat.

In Cutler's case, a slide from the tumor in which we had the opportunity to study, the arrangement of the cells was different. Here they formed large masses, filling in a meshwork made of capillaries. Fibrous tissue was scant. A moderate number of cells were clear, owing to their fat content. Most cells, however, contained an abundance of eosinophilic, granular cytoplasm. The nuclei were large, of uniform size and oval or round, with a distinct nuclear membrane, evenly distributed granular chromatin and a distinct nucleolus. None of the nuclei were displaced. Microscopically therefore, a difference existed between the tumor in Cutler's and those in the other 2 cases. The same is true of the histologic appearance in the cases reported by Benda and Krause and by Plate. In the former authors' case the tumor cells were arranged in various patterns: diffuse masses, rosette-like structures and long columns. Many cells appeared frothy and clear, owing to their fat content. In Plate's case the tumor cell was essentially cylindric and filled with fat. The cells were arranged in various patterns: rosettes, columns and alveoli. In both cases the growths were evidently of the granulosa cell type, the tumor cells being filled with lipoid.

After we had reviewed all these cases it appeared evident that the histologic pattern of the growths was variable, making it difficult to identify the tumors as similar on a histologic basis alone. This difficulty pertained particularly to the first 3 cases (Wolf; Wills and Romano; Cutler), the others being more easily identified as instances of granulosa cell tumor. If the first 3 tumors were similar to the others, then they

also were granulosa cell tumors, differing only in the degree of fatty change, and should be classified as such and not as corpus luteum tumors. Whether the fatty change was due to the luteinizing factor responsible in changing normal granulosa cells into those constituting corpus luteum is of course something one can only philosophize about. Nevertheless, if that should be the case, one would have a reasonable basis for expecting the variable histologic picture of the group, for then it could be ascribed to different degrees of differentiation of a tumor whose histologic picture to begin with is variable.

The confusion of names that exists is understandable. The 5 feminizing tumors, like the masculinizing growths, bore a superficial resemblance to corpus luteum, from which many have been named. However, the biologic effects of the two types of tumor were so different and were so unlike those associated with the corpus luteum that it is dangerous to regard them as both arising from this body. It would simplify matters if it were possible to adopt some acceptable and appropriate name for the masculinizing tumor. If its origin from adrenal gland were certain, it should be called an adrenal hypernephroma rather than a hypernephroid. Since this matter is in dispute, we suggest a name descriptive of its biologic properties—masculinovoblastoma. This differentiates the growth from the other masculinizing tumor, the arrhenoblastoma, and the femininizing one, more appropriately referred to as a luteinized granulosa cell growth.

Though the masculinovoblastoma may be primarily responsible for stimulating growth of hair, hypertrophy of the clitoris and inhibition of factors which play a role in the menstrual cycle, there is reason to feel that there is an interplay with the pituitary gland. This is suggested by the fact that although menstruation returns promptly after operation, the effect on hirsutism is not so complete. To be sure, changes in texture and in rate of growth begin in some cases promptly; nevertheless, the hairs still grow even after one and a half years. In other words, the stimulating factor still persists. Other evidence suggesting outside influences is also present. Several of the patients had disturbances in carbohydrate metabolism, as shown by glycosuria, hyperglycemia and a diabetic type of dextrose tolerance curve, which might be explained on the basis of diminished pituitary action. Most interesting is the fact that a dextrose tolerance curve obtained in our case six months after the tumor was removed was still abnormal, indicating a continuing action of a factor outside the ovary, most likely pituitary. Polycythemia, present in several cases, suggests the same possibility. Moehlig and Bates [33] reported 2 cases of polycythemia in persons with pituitary basophilism. Further evidence to support an ovarian tumor–pituitary interplay was added by

33. Moehlig, R. C., and Bates, G. S.: Influence of the Pituitary Gland on Erythrocyte Formation, Arch. Int. Med. **51**:207 (Feb.) 1933.

Norris,[34] who reported on the autopsy in a case of arrhenoblastoma. He described degranulation and hyalinization of the cytoplasm of the basophils in the pituitary gland. According to Crooke,[35] this change is seen more regularly in pituitary basophilism than is adenoma formation.

This interplay of a gland with the pituitary body is not at all unique for the ovary. It was suggested by Graef and associates [36] in a report of hirsutism, obesity and hypertension in a girl with adrenal carcinoma. The pituitary gland in that case likewise showed peculiar changes in the granules of the basophils.

SUMMARY

A new group of ovarian tumors associated with masculinization, different from the arrhenoblastoma, has been recognized for some time.

Seven cases reported in the literature are accepted as examples of this tumor. The 2 reported here bring the total to 9.

In only 1 case was the growth proved malignant.

Removal of the tumor results in recession of symptoms.

The histogenesis of the tumor is in doubt. There is much to favor its origin from an adrenal rest. Some authors, however, lean to a luteinic origin.

The tumor was unilateral (in 8 of 9 cases), solid yellow or orange, composed of large cells and in some cases clear owing to fat content, while in others, in which no fat was present, the cytoplasm was not clear.

The pathologic differentiation between the masculinizing tumor and the femininizing luteoma may be difficult.

It is suggested that the term masculinovoblastoma be adopted for the masculinizing tumor, to distinguish it from the arrhenoblastoma and the femininizing luteoma.

Clinical evidence suggests an interplay of the growth with the pituitary gland.

NOTE.—Since May 1938, when this article was submitted for publication, the following events have occurred to our patient:

On June 7 she presented herself in the outpatient department because she had failed to menstruate in May. Finding an enlarged, soft uterus, the examiner made a diagnosis of pregnancy. A Friedman pregnancy test performed three days later gave a positive result. A dextrose tolerance test on this day showed 68 mg.

34. Norris, E. H.: Arrhenoblastoma, Am. J. Cancer **32**:1, 1938.

35. Crooke, A. C.: Changes in the Basophilic Cells of the Pituitary Gland Common to Conditions Which Exhibit the Syndrome Attributed to Basophilic Adenoma, J. Path. & Bact. **41**:339, 1935.

36. Graef, I.; Bunim, J. J., and Rottino, A.: Hirsutism, Hypertension and Obesity Associated with Carcinoma of the Adrenal Cortex: Indeterminate Pituitary Adenoma and Selective Changes in Beta Cells (Basophils) of Hypophysis, Arch. Int. Med. **57**:1085 (June) 1936.

of sugar per hundred cubic centimeters of blood during fasting, 108 mg. one half hour after the ingestion of 100 Gm. of dextrose, 137 mg. after one hour, 58 mg. after two hours and 88 mg. after three hours.

She was not seen again until August 19, when severe ureteral colic forced her to return to the hospital. It was elicited that she had had a normal menstrual period on June 19, on July 17 and a few days before the current admission. All periods had been normal. She was firm in her denial that an abortion had been induced. It was further elicited that she was gaining weight and had to shave with increasing frequency. Pelvic examination now revealed a normal-sized uterus. A small, tender mass was felt in the left adnexal region. The status of hirsutism was the same as at the first admission, with the exception that the hairs were finer and lighter. Friedman tests on this admission gave repeatedly negative results.

On September 14 the left tube and ovary were removed. The latter was found adherent in the cul-de-sac. She recovered from her operation and was discharged on October 16. In the interval that followed she suffered from hot flashes and headaches, which were controlled more or less by administration of estrogenic substances. Of particular interest was the definite change in the rate and character of growth of hair. For the first time since any operative intervention had been made she was able to postpone shaving for six weeks, until November 22. When next seen, on December 2, she had not shaved. She appeared slimmer, the texture of the skin was soft and smooth, and the facial hairs, though increased, were much lighter and finer than theretofore. On March 21, 1939, she presented herself on request. She weighed 150 pounds (68 Kg.) and appeared moderately obese. The rate of growth of facial hair had increased so that she shaved every other day.

We wish to note further that two other papers[37] dealing with the ovarian tumor in question in addition to those already referred to have appeared.

Pathologic Report.—The specimen consisted of a tube and ovary with its mesentery. The tube appeared normal except for a few peritoneal adhesion tags. The ovary was of normal size, measuring 32 by 35 by 15 mm. and weighing 12.3 Gm. The surface was smooth and nodular, owing to the presence of eight thin-walled cysts filled with clear straw-colored fluid. One contained blood. They measured from 4 by 3 to 7 by 3 mm. Two bodies were found adjacent to each other, measuring 6 by 3 and 6 by 2 mm., respectively. Each had a thin, wavy, golden-yellow margin 1 mm. thick. The center of one was cystic and that of the other solid, being occupied by a gray fibrous tissue. In addition, there was a third body 7 by 3 mm. close to the surface, with an orange-colored margin and a gray fibrous core. Macroscopically all three were interpreted as regressing corpora lutea.

The entire ovary was cut into serial blocks, and histologic sections were made from each. Microscopic examination of these showed many primordial follicles with normal-appearing ova. The cysts noted grossly were seen to be of the theca lutein variety. The yellow bodies were composed of large irregular clear cells similar to those composing the tumor removed with the first ovary. There were no features, however, distinguishing them from cells of regressing corpus luteum. It was concluded, therefore, on anatomic grounds that in this ovary the yellow bodies were corpora lutea.

Dr. Franz Yost collaborated in this study.

37. Novak, E.: Masculinizing Tumors of the Ovary (Arrhenoblastoma, Adrenal Ovarian Tumors), Am. J. Obst. & Gynec. **36**:840, 1938. Reis, R. A., and Saphir, O. S.: Masculinizing Elements in the Ovary, ibid. **35**:954, 1938.

THE PRECORDIAL LEAD

I. FINDINGS FOR PATIENTS WITH NORMAL HEARTS AND THOSE WITH HEART DISEASE OTHER THAN MYOCARDIAL INFARCTION

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Since the introduction of the use of the precordial lead in clinical electrocardiography, as the result of the work of Wilson [1] and of Wolferth and Wood,[2] enough data have been accumulated to establish it as a helpful and at times necessary procedure in the diagnosis of cardiac disorders. But as frequently occurs with any new procedure, further study becomes essential to define its limitations and its proper value. After the three conventional leads were first introduced into general use, physicians had to become familiar with the wide range of variations in normal electrocardiograms before they could interpret any abnormality. Moreover, it was quickly found that many factors besides disease of the heart could alter the form of the tracings. Among these factors were the effect of digitalis and of the drinking of ice water on the T wave and the alterations that resulted from deep breathing, from the presence of fluid in either pleural cavity or from a change in the position of the body. In fact, significant abnormalities were found to result from other causes, such as disturbances in the calcium or bodily

From the Medical Clinic of the Peter Bent Brigham Hospital.

Read in part at the meeting of the New England Heart Association, Boston, Jan. 24, 1938.

1. Wilson, F. N., in discussion on papers of Koltz and Lloyd; Warthin; Conner and Holt; Scott, Feil, Katz and Moore, and Carter, Tr. A. Am. Physicians **45**:168, 1930. Wilson, F. N.; Barker, P. S.; Macleod, A. G., and Klostermyer, L. L.: The Electrocardiogram in Coronary Thrombosis, Proc. Soc. Exper. Biol. & Med. **29**:1006, 1932. Wilson, F. N.; Macleod, A. G., and Barker, P. S.: The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissues, University of Michigan Studies, Scientific Series, Ann Arbor, Mich., University of Michigan Press, 1933, vol. 10, p. 22.

2. Wolferth, C. C., and Wood, F. C.: The Electrocardiogram in Coronary Thrombosis, Am. J. M. Sc. **183**:30, 1932.

metabolism accompanying diseases of the endocrine glands, e. g., myxedema, hyperthyroidism, hypoparathyroidism and hyperparathyroidism. It is evident, therefore, that similar studies are now necessary to ascertain the changes that occur in the precordial lead under a great variety of circumstances. Only in this way can reliable and decisive criteria be established that will aid in the diagnosis of myocardial infarction. For it is with respect to this condition that the precordial lead is proving to have its main value.

Technical difficulties have already arisen and likely will continue to do so to some extent, for they are inherent in this new method. Whereas with the three conventional leads it mattered little or not at all which part of the forearm or left leg was employed or even what the size of the electrode was, it quickly became clear that slight variations in the exact location over the precordium to be explored produced profound changes in the form of the electrocardiogram. From a practical point of view, it becomes highly desirable, if possible, to have not only a uniform procedure but one that is simple and that elicits all the significant data.

METHOD OF STUDY

As the main purpose of this study was to find one optimum point over the precordium from which lead IV should be taken, a series of 9 or 10 tracings were obtained from different parts of the chest. The points selected are indicated in figure 1. It was hoped thereby if possible to find a single position which would show significant alterations when myocardial infarction was present and would fail to show such changes when myocardial infarction was absent. It is obvious that the point of preference would be that place at which under normal circumstances the deflections of the electrocardiographic waves are greatest, for it is the inversion or the absence of these same waves that lays the foundation for the detection of the presence or absence of myocardial infarction. By this means the significance of minor alterations becomes less confusing.

The three features that were particularly studied were the absence or amplitude of the Q wave, the direction and amplitude of the T wave and the deviation of the ST segment from the isoelectric line. These three aspects of the electrocardiograms were investigated because they are the ones that have been studied and found to be useful in the making of a diagnosis. It is our purpose to focus attention on the preference and reliability of the data obtained from around the apex of the heart, i. e., the eighth and ninth positions.

For all the tracings the old polarity was used, with the right arm electrode as the exploring electrode at the precordium and the left leg

electrode as the indifferent electrode.[3] The electrode used was of the standard German silver type, measuring 1½ by 2 inches (3.8 by 5 cm.), and its long diameter was placed parallel to the long axis of the body. We secured 526 tracings for 352 patients. Sixty-four of these patients subsequently came to autopsy, and we had the opportunity of correlating the electrocardiographic findings with the postmortem data.

For purposes of this study it is required that a normal precordial tracing should have a Q wave of 2 mm. or more and an inverted T wave. A tracing was regarded as indicative of myocardial infarction if the Q wave was absent. It was regarded as questionably indicative if the

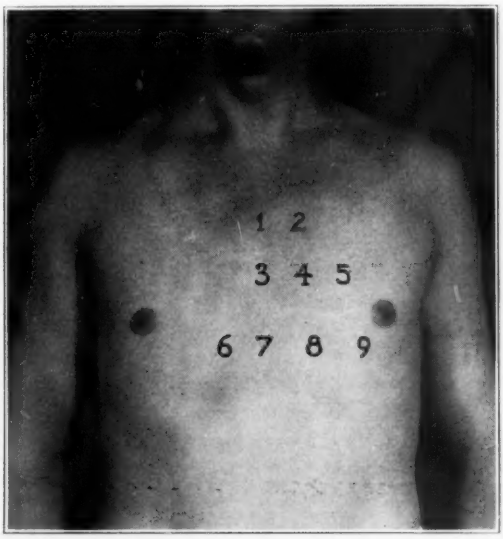

Fig. 1.—The numbers indicate the nine position from which the precordial leads were taken throughout this study. *1* indicates the position in the midline in the second interspace; *2*, 4 cm. to the left of the midline in the second interspace; *3*, *4* and *5*, in the midline, 4 cm. and 8 cm., respectively, to the left between the third and fourth interspaces; *6*, 4 cm. to the right in the fifth interspace, and *7*, *8* and *9*, in the midline, 5 cm. and 10 cm., respectively, to the left in the fifth interspace.

Q wave measured less than 2 mm. The term abnormal was used when a normal Q wave was present but the T wave was upright. Further-

3. Since this study was completed it has become the custom to reverse the polarity in taking lead IV, so the reader may need to look on the curves accompanying this article as opposite to those that are now being obtained (mirror image).

more, curves were regarded as indicative of myocardial infarction during the acute stage of the disease if the ST segment was decidedly elevated or depressed.

FINDINGS FOR NORMAL HEARTS

A group of 55 young, normal, healthy nurses and house officers and 20 house patients who showed a normal condition of the heart at autopsy were studied. The patients examined post mortem died of conditions in no way related to the cardiovascular system. Analysis of the Q wave with each position showed that it was definitely deeper with the eighth and ninth positions than with any other position over the precordium and that the ninth position gave an average Q wave 1 mm. deeper than that with the eighth position (table 1). In utilizing the presence or absence of the Q wave as indicative of myocardial infarction, the apical position is therefore preferable, because normally it is always determinable and there is the greatest excursion at this point.

It has been thought by some observers that a Q wave of less than 2 mm. needs to be regarded with suspicion and is questionably indicative of myocardial infarction. This aspect was investigated in relation to the occurrence of a small Q wave in normal electrocardiograms. The frequency of a small Q wave in the electrocardiograms of 75 normal persons is shown in table 2. One can easily see that the chance placement of the electrode along or to the right of the sternum might have given a small Q wave or one questionably indicative of myocardial infarction in 5 to 20 per cent of these cases but that no such confusion would have resulted if the eighth or ninth position (or a position around the apex) had been used. For here a normal Q wave was always obtained. Since 9 chest leads were made for each of these 75 persons, 675 chest leads were studied. There were only 7 instances in which the Q wave was absent, and in each of these cases the electrode was placed over the base of the heart and not at the apex. Absence of the Q wave is therefore rare when the heart is normal.

In analyzing the form of the T wave obtained for these normal persons, a position was sought which normally would give an inverted wave, for an upright wave has been regarded as indicating a pathologic condition. It was found that with no position was the T wave invariably inverted. However, it was much more frequently upright with the first seven positions than with the eighth or ninth (table 2). It follows that the chance of obtaining an upright T wave when the electrode is placed along the sternum is great. In fact, with some leads, e. g., from the right of the sternum, it appears to be normally upright rather than inverted. Several of these normal persons showed a definitely upright T wave with every precordial lead except the ninth, as illustrated in

TABLE 1.—*The Amplitude of the Q and T Waves with Various Precordial Leads*

TABLE 1.—*The Amplitude of the Q and T Waves with Various Precordial Leads*

Condition	Number of Cases		Precordial Positions									
			1	2	3	4	5	6	7	8	9	Apex
Q Waves												
Normal (young persons)	55	Percentage of small Q waves.....	18	5	1.8	1.8	3.6	10	5	0	0	.....
		Range of Q waves, mm.....	0-7	1-10	1-8	1-11	1-11.5	1-6.5	1-9	2-13	2-13	.....
		Average depth, mm.....	3.69	4.23	4.21	5.05	4.6	2.76	4.47	5.26	6.3	.....
Normal heart (autopsy)	20	Percentage of small Q waves.....	25	30	20	15	15	45	15	0	0	.....
		Range of Q waves, mm.....	0-5.5	0-7	0-4.5	1-8	1-11	1-8	0.5-15	2-12	2-20	.....
		Average depth, mm.....	2.36	2.94	3.1	3.64	4.1	1.96	3.83	5.05	7.09	.....
Mitral stenosis	10	Percentage of small Q waves.....	50	40	40	40	40	40	40	30	0	.....
		Range of Q waves, mm.....	0-5	0-7	0-8	0-10	0-8	0-6	0-9	1.5-12	3-12	.....
		Average depth, mm.....	3.1	3.5	4.2	5.07	4.2	2.78	4.92	5.92	6.82	.....
Syphilis	5	Percentage of small Q waves.....	80	80	80	80	60	60	80	60	40	20
		Range of Q waves, mm.....	0-2	0-2.5	0-2	0-2.5	0-3	0-1	0-2.5	0-4.5	0-9	0.5-11
		Average depth, mm.....	0.6	0.8	0.6	0.8	1.1	0.4	0.8	1.9	3.2	4.9
Hypertension	13	Percentage of small Q waves.....	69	61	69	46	30	69	46	23	15	0
		Range of Q waves, mm.....	0-11	0-14	0-13	0-22	0-24	0-6	0-12	0-20	0-28	2-26
		Average depth, mm.....	1.9	2.6	2.1	2	1.6	0.41	1.33	2.08	4.41	15.7
Uremia	10	Percentage of small Q waves.....	50	41	50	33	33	58	25	0	0	0
		Range of Q waves, mm.....	0-6	0-7	0-8	0.5-11	1.5-9	0-4	1-7.5	2-11	2-9	3-9
		Average depth, mm.....	1.9	2.75	2.6	3.83	4	1.66	2.9	4.33	4.6	6
Subacute bacterial endocarditis	4	Percentage of small Q waves.....	25	30	20	15	15	45	15	0	0	.....
		Range of Q waves, mm.....	0-5.5	0-7	0-4.5	1-8	1-11	1-8	0.5-15	2-12	2-20	.....
		Average depth, mm.....	2.36	2.94	3.64	3.64	4.1	1.96	3.83	5.05	7.09	.....
T Waves												
Normal (young persons)	55	Percentage of upright T waves.....	67	41	43	16	10	76	25	9	1.8	.....
		Highest wave, mm.....	5	3.5	1.5	1	6	1.5	1	1.5	1.5	.....
		Deepest wave, mm.....	4	7	15	12	2	9	13.5	9.5	10	.....
Normal heart (autopsy)	20	Percentage of upright T waves.....	65	60	45	30	25	50	40	10	15	.....
		Highest wave, mm.....	4	3.5	2	2	2.5	2.5	2	1	1.5	.....
		Deepest wave, mm.....	3	6.5	8.5	7	6.5	3	3.5	5	3.5	.....
Mitral stenosis	10	Percentage of upright T waves.....	50	40	40	30	30	60	30	40	30	.....
		Highest wave, mm.....	4	3.5	2.5	2.5	2.5	3	4.5	4	2	.....
		Deepest wave, mm.....	1.5	1.5	3	6	6	1	5.5	8	10	.....
Syphilis	5	Percentage of upright T waves.....	40	40	10	10	0	10	0	0	0	10
		Highest wave, mm.....	2	1	1	1.5	0	3	0	0	0	1.5
		Deepest wave, mm.....	3	4	5	6	5	4	5	7	5	4.5
Hypertension	13	Percentage of upright T waves.....	46	46	53	38	46	69	38	15	0	15
		Highest wave, mm.....	3.5	3	4.5	2.5	3	2.5	5	2.5	0	3.5
		Deepest wave, mm.....	4.5	4	3.5	4.5	6	6	10	9.5	12	9
Uremia	10	Percentage of upright T waves.....	40	40	40	30	60	40	20	50	50	50
		Highest wave, mm.....	5	4	6	3	2	5	5	3	3	2
		Deepest wave, mm.....	5	5	4	4	4	4	8	7	7	7
Subacute bacterial endocarditis	4	Percentage of upright T waves.....	80	40	60	40	40	80	80	40	0	0
		Highest wave, mm.....	3.5	2	2	2	1.5	3	3.5	4	0	0
		Deepest wave, mm.....	0.5	1.5	1	2	3	2	0	2.5	4.5	6

figure 2. In only 4 cases was the T wave upright with every precordial position, and in these cases the lowest T wave was obtained with the apical position (figs. 3 and 4). There is likelihood of finding an upright T wave with the apical position when the heart is normal, but it is small. Besides the fact that the T wave was more frequently inverted with the apical position, the wave averaged about 1 mm. deeper with this position than with any other precordial lead.

In our study of 75 normal persons the Q wave was invariably present and was deeper with the apical position than with any other precordial position. Likewise, the T wave, with rare exceptions, was inverted and deepest with the apical position. Therefore, it seems reasonable to assume that if the criteria of myocardial infarction are the absence of the Q wave and the presence of an upright T wave, the apex is the point from which the chest lead should be obtained.

TABLE 2.—*Frequency of Small Q Waves* and Upright T Waves with Various Precordial Positions in Seventy-Five Cases in Which the Heart Was Normal*

Precordial Position	Occurrence of Small Q Waves		Range of of All Q Waves, Mm.	Occurrence of Upright T Waves	
	Number of Instances	Percentage		Number of Instances	Percentage
1	15	20	0-9	50	66
2	9	12	1-11	35	46
3	4	5	1-10	33	44
4	4	5	1-15	15	20
5	5	6	1-18.5	11	14
6	15	20	0.5-8	52	69
7	6	9	1-9	22	29
8	0	0	2-18.5	7	9
9	0	0	2-19	4	5

* Less than 2 mm.

EFFECT OF VARIOUS PHYSIOLOGIC AND PATHOLOGIC CONDITIONS ON THE PRECORDIAL LEADS FOR NORMAL PERSONS

Respiration.—It has been observed that small variations in the depth of the Q wave may occur, and they seem to follow the respiratory cycle. We therefore studied the effect of respiration on the fourth lead. Tracings were taken for 2 normal young males during deep inspiration and in complete expiration with each of the nine positions. With every position the Q wave was deeper during expiration than during inspiration. The increase in the depth of the wave varied from 1 to 3.5 mm. Five other normal young persons were observed during a complete respiratory cycle, which consisted of a deep inspiration that was held for several seconds and then complete expiration followed by normal breathing. Inspiration shortened the Q wave in 4 instances and the T wave in 2 instances in the tracings obtained with the apical lead. In 1 case the T wave went from 1.5 mm. inverted to 1.5 mm. upright, and the

Q wave changed from 4 to 1 mm. in depth during held inspiration. This curve could have been interpreted as questionably indicative of myocardial infarction during this period. After expiration each tracing returned to its previous appearance. This was most likely due to the

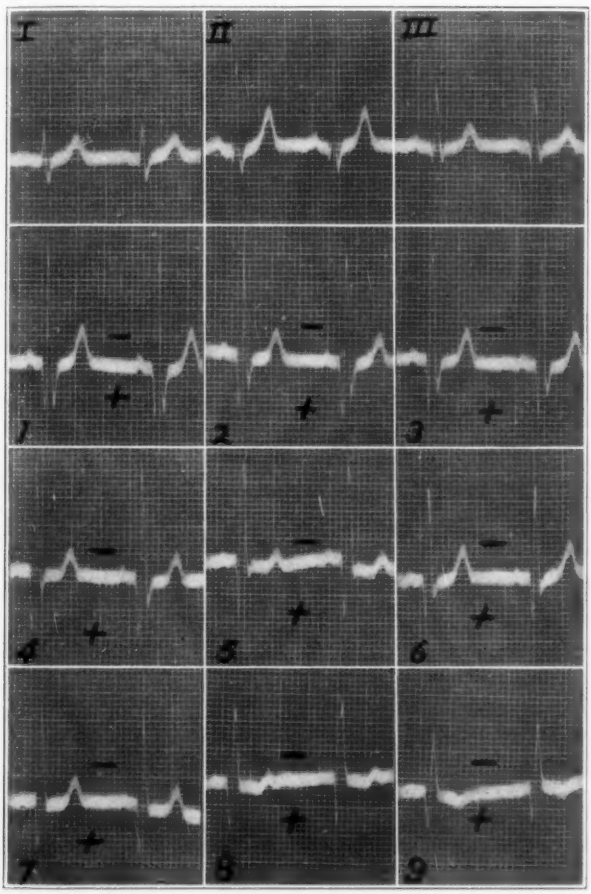

Fig. 2.—The first 3 curves are the conventional leads obtained for a normal person. The remainder are the tracings obtained with the nine precordial positions. Note the presence of an upright T wave in all leads except the last, taken from the apex.

raising and lowering of the apex of the heart during marked respiratory motion. In 2 cases in which there was an upright T wave with the apical

position, the height of the T wave increased during inspiration. One patient showed a Q wave only with the apical position, and there it varied from 0 to 2.5 mm. and seemed to follow the respiratory cycle. The curves were interpreted as normal. This patient came to autopsy a few days later, and the heart, coronary arteries and myocardium were normal. It seems that more reliable information as to Q_4 would be obtained if tracings were taken during normal breathing and certainly not during deep inspiration.

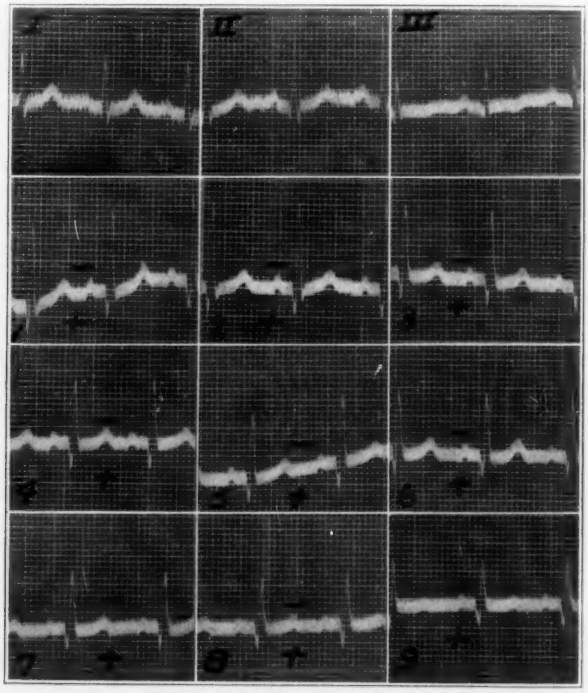

Fig. 3.—The first 3 curves are the conventional leads obtained for a normal person. The remainder are those obtained with the nine precordial positions. Note the presence of an upright T wave in all leads, the lowest being in the apical lead.

Ice Water.—Tracings were taken for 2 normal young men just prior to and immediately after the drinking of 1,200 cc. of ice water. The Q wave with the apical lead was definitely decreased, from 15 to 11 cm. in 1 case and from 21 to 8 mm. in another, after the ingestion of ice water. No significant changes were noted in the T wave.

Position.—During this study it was necessary to make tracings for orthopneic patients while they were sitting down. In order to investigate the effect of posture, the nine chest positions were used for each of 5 young healthy persons while they were on the back and on the right and left side as well as in the sitting position. There were no significant

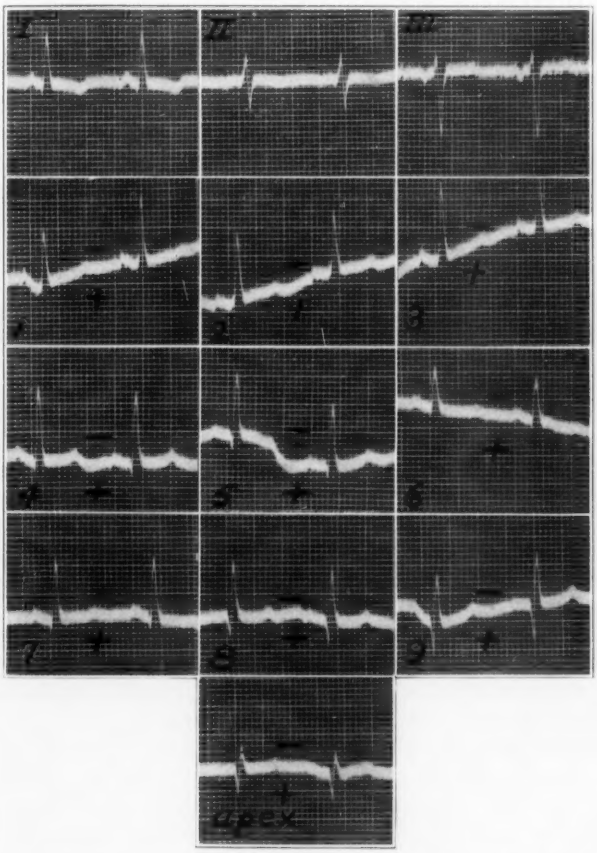

Fig. 4.—The first 3 curves are the conventional leads obtained for a patient who died of carcinomatosis. Autopsy showed a normal heart. The other curves are the precordial leads. Note the upright T waves in all the precordial leads.

changes in the tracings except in 2 instances, in which the upright element of the QRS entirely disappeared, with an increase in the downward deflection. One of these tracings occurred when the subject was

changing from the right to the left lateral position and the other when he was changing from the prone to the sitting position. There were slight changes in the depth of the Q and T waves with the various positions, but the apical position gave a normal curve in each case, whether the patient was on his back, on his right or left side or sitting up. We believe that if the apical position is used, the value of the interpretation will remain constant, regardless of whether the patient is in the prone or the sitting position.

Fluid in the Left Side of the Chest and Abdomen and Collapse of the Lung.—Curves were made for 6 patients before and after the removal of fluid, varying in amount from 250 to 2,000 cc., in order to determine the effect of fluid in the left pleural space on the precordial tracing. The Q and R waves with the apical position were definitely increased in each case after the removal of the fluid from the left pleural space. The greatest single increase in the Q wave was 11.5 mm. after the removal of 2,000 cc. of fluid. In 1 case curves were made with the apical position before and after removal of 2,000 cc. of fluid, and it was found that there was no Q wave before thoracentesis and that there was a 7 mm. Q wave after tapping. The response of the T wave was variable. If it was upright before thoracentesis, it might remain upright or become inverted. If it was inverted before thoracentesis, it might remain inverted or become upright. We believe that if fluid is present in the left pleural cavity the interpretation of the fourth lead should be held in reserve, as an absent or small Q wave may become normal after thoracentesis.

There were 2 patients with tuberculosis of the left lung, one of whom was treated by complete thoracoplasty on the left and the other by injection of oil into the pleural cavity. Each had complete collapse of the left lung. With many of the precordial leads the Q wave was less than 2 mm.; but with the electrode at the apex it was normal in each case, and the T wave was inverted. One patient with spontaneous pneumothorax on the left side also had a normal fourth (apical) lead. Master and his associates[4] noted the complete absence of Q_4 in 2 cases of spontaneous pneumothorax, with return of the Q wave on absorption of the pneumothorax and reexpansion of the collapsed lung.

Removal of a large amount of abdominal fluid, e. g., 14,000 cc., has been observed to change a questionably positive Q wave before tapping to a normally deep Q wave (10 mm.) after paracentesis. One patient who showed this sequence came to autopsy later and had a normal myocardium.

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4. Master, A. M.; Dack, S.; Kalter, H. H., and Jaffe, H. L.: The Significance of an Absent or a Small Initial Positive Deflection in the Precordial Lead, Am. Heart J. **14**:297, 1937.

Pulmonary Conditions.—Precordial tracings taken for several patients with pneumonia of the lower lobe of the left lung were normal throughout. There were, however, 2 instances in which the Q wave was present only with the apical lead, being 4.5 and 1.5 mm., respec-

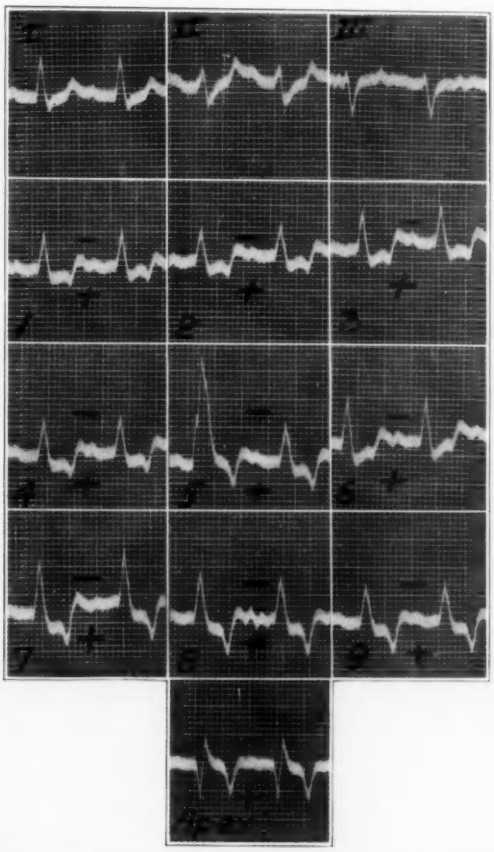

Fig. 5.—Tracings for a patient with pneumonia of the lower lobe of the left lung and aortic stenosis. Autopsy showed no myocardial infarction. Note the absence of a Q wave in all leads except the apical.

tively (fig. 5). In the latter case the curve was interpreted as questionably indicative of myocardial infarction. Both patients were examined post mortem, and no cardiac infarction was present.

Four patients with pulmonary infarction of both the right and the left lung were studied prior to death. The Q wave was normal

with the apical lead in each case. The only abnormality noted was an upright T wave with a slightly high take-off in each precordial lead for a patient with an infarct of the middle lobe of the right lung. None of these 4 patients showed a myocardial infarct post mortem. One patient with bronchogenic carcinoma of the lower lobe of the left lung who at autopsy showed no heart disease had a normal Q and an upright T wave with each precordial position. Here, again, the tracing obtained with the apical position was the most reliable of all.

PATHOLOGIC HEARTS WITHOUT MYOCARDIAL INFARCTION

Mitral Stenosis.—Ten patients with mitral stenosis were studied; 7 of them had regular rhythm, and 3 had auricular fibrillation. The latter 3 were examined post mortem and showed no disease of the coronary arteries or myocardial infarction. In none of the 10 cases was there any clinical evidence of angina pectoris. In the study of the various positions over the precordium, a small Q wave, of less than 2 mm., was found frequently (30 to 50 per cent) with all the positions except the apical. In all the cases the apical position gave a normal Q wave. There were 3 instances in which the Q wave might have been regarded as questionably indicative of myocardial infarction with all positions except the apical (fig. 6). An analysis of the form of the T wave showed it to be upright in 30 to 60 per cent of the cases with all positions, including the apical (table 1). However, the average depth of the T wave was greatest with the apical position. The T wave was upright throughout for 2 patients, one of whom was examined post mortem. Neither had angina clinically, and the patient who died had normal coronary arteries at autopsy.

It is interesting that the P wave in 3 of the cases of mitral stenosis was prominent and upright with nearly all the chest leads, more so when the electrode was near the base of the heart than when it was at the apex. It follows that in cases of mitral stenosis the alteration of the T wave is of practically no value in the diagnosis of myocardial infarction and the apical position must be used to interpret the significance of the Q wave.

Syphilitic Heart Disease.—There were 4 patients with syphilitic heart disease in this series, all of whom were examined post mortem. The first had syphilitic aortitis with aortic insufficiency and died of congestive heart failure. The precordial electrocardiograms were entirely normal. A second had syphilitic aortitis and showed no Q wave except with the ninth and apical positions, when it measured 2 and 3 mm., respectively. The heart showed no narrowing of the coronary orifices, and the myocardium was normal. The 2 remaining patients had

definite narrowing of the coronary orifices but no coronary thrombosis or myocardial infarction. One of the 2 had definite angina pectoris for three years and showed considerable diffuse fibrosis of the myocardium. Neither of these patients showed a Q wave except in the

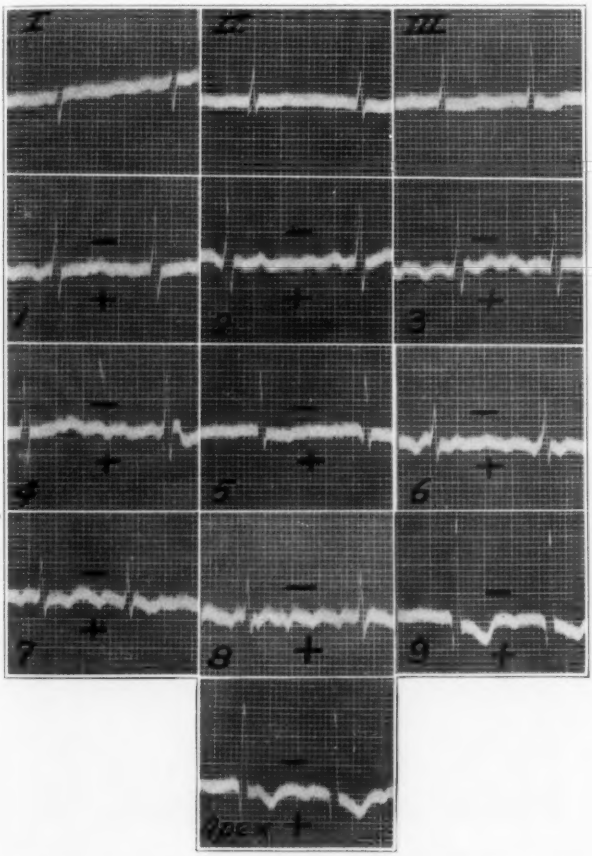

Fig. 6.—Tracings for a patient with mitral stenosis, auricular fibrillation and multiple pulmonary infarcts. Autopsy showed no myocardial infarction. Note that the Q wave is absent in all precordial leads except the ninth and apical leads.

apical lead, where it was only 0.5 mm. (fig. 7). One may conclude that syphilitic narrowing of the coronary orifices, without coronary thrombosis of myocardial infarction, may be associated with a small Q wave.

Hypertensive Heart Disease.—This group included 13 patients, 7 of whom were examined post mortem. All had hypertension, and none had angina pectoris or a history of an acute coronary episode. Those studied post mortem did not have myocardial infarction. A small or questionably positive Q wave occurred frequently with the first eight

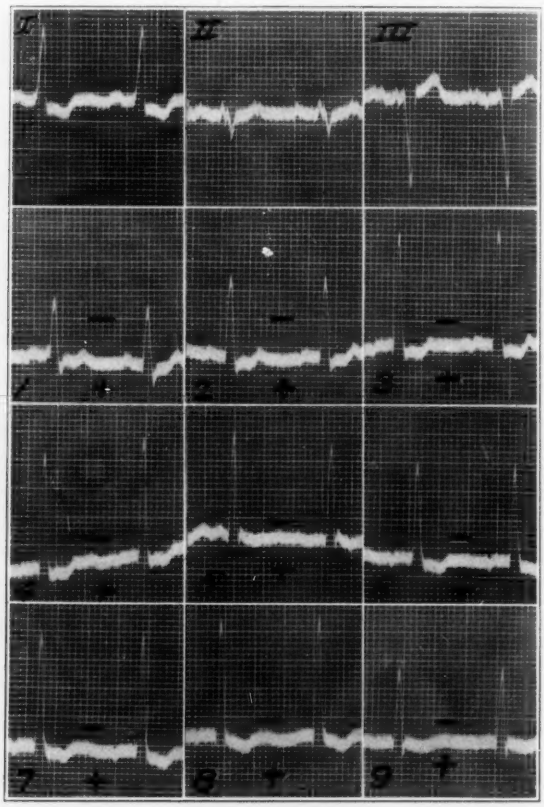

Fig. 7.—Tracings for a patient with syphilitic aortitis with angina pectoris. Autopsy showed marked narrowing of the coronary ostia without myocardial infarction. Note the absence of the Q wave except for a 0.5 mm. wave in the apical lead.

positions over the precordium. The incidence of such small waves varied from 23 to 69 per cent with the different positions. With the ninth position, however, there were only 2 such cases, and with the apical position there were none. In fact, when the heart is enlarged

the Q wave with the apical position may be deep, and the change from a small to a prominent wave may take place abruptly with a change from the eighth or ninth position to the apical. In an especially interesting case (fig. 8) there was an initial upward deflection before the Q

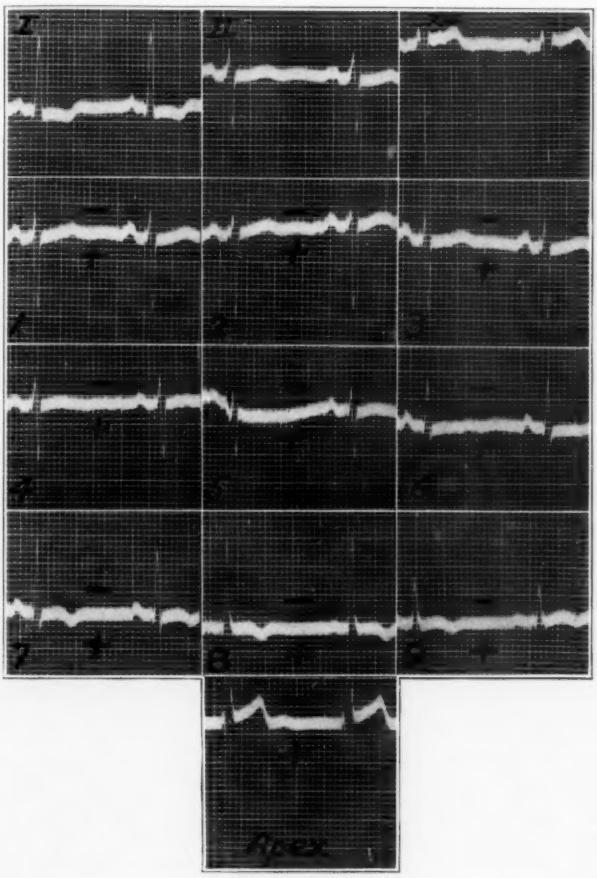

Fig. 8.—Curves for a patient who died of hypertensive heart failure. Autopsy showed no myocardial infarction or coronary thrombosis. Note that a small initial upright wave followed by a prominent downward wave does not indicate absence of the Q wave. The seventh, eighth and ninth leads show no Q wave, but a slight movement of the electrode toward the apex revealed a deep Q and an upright T wave.

wave of 3 or 4 mm. in several of the precordial leads. In the seventh, eighth and ninth leads there was no Q wave, and the T wave was

inverted. Slight movement of the electrode toward the apex, however, produced after a slight upward deflection a Q wave of 26 mm. and an upright T. Autopsy revealed no coronary thrombosis or infarction. It is significant that the slight initial upward deflection when followed by a prominent downward wave was not to be interpreted as indicating absence of the Q wave.

Analysis of the form of the T wave in these cases of hypertension showed that it was frequently upright (15 to 69 per cent) with the first eight positions, but in no instance was it upright with the ninth position. However, in 2 of the 13 cases, curves obtained from the apical impulse which was beyond the nipple line showed an upright T wave. These last 2 cases are important, because if the curves had been obtained only from the region of the nipple or midclavicular line they would have shown no Q and an inverted T wave and thereby would have been interpreted as indicative of infarction when none was present. It follows that, particularly when the heart is large, the precordial lead should be taken from the region of the apical impulse, for although the T wave may be upright the Q wave will be present. In fact, in many instances in which there is marked left axis deviation but no myocardial infarction, there are inverted T_1 and upright T_3 waves with the 3 conventional leads and a distinctly upright T wave with the apical position.

Subacute Bacterial Endocarditis.—Our experience with 4 patients with subacute bacterial endocarditis who were examined post mortem was in accord with the general findings obtained when the heart is normal. The Q wave was either absent or small, and the T wave was upright in many of the leads except the apical. There was 1 instance in which the T wave was downward, and two months later, just a few days before death, it became upright with the first eight positions but was still inverted with the apical position. At autopsy there was a small mural thrombus in the posterior wall of the left ventricle which was an extension from the bacterial endocarditis of the mitral valve.

Uremia.—There were 10 patients with uremia, 5 of whom were examined post mortem. Three of the 10 were under 25 years of age. Although there were frequent variations in the form of the Q and T waves with various precordial leads, the Q wave was invariably normal with the apical position, but the T wave was just as often upright as inverted. This group of patients showed the highest incidence of curves with an upright T wave with the apical position (50 per cent). The pericarditis so frequently associated with uremia seemed to have no effect on the direction of the T wave with the apical position. The T wave has been observed upright and inverted with the apical position in the curves for patients with and without pericarditis.

DISTURBANCE IN THE MECHANISM OF THE HEART BEAT

Auricular Fibrillation.—In cases of auricular fibrillation one often sees noticeable variation in the depth of the Q wave in successive beats. Also, the so-called f waves may distort the T wave so that it may appear upright in some complexes and diphasic or inverted in others. Furthermore, the depth of the T wave may vary in different cycles. Four persons with normal hearts who had transient periods of auricular fibrillation were studied. They each showed a normal fourth lead during both rhythms. The only variation was the altered depth of the Q and T waves in different cycles. There were 22 additional patients with fibrillation and various forms of heart disease, and 5 of them were studied post mortem. Each of the latter had a normal Q wave with the apical position, and none of them showed myocardial infarction. Of the remaining 17, 4 either had no Q wave or had a small one with the apical position, and in each instance there was a fairly satisfactory history of old or recent coronary thrombosis. The 13 other patients all showed a significant Q wave, and only 1 of them had a history of an acute coronary episode. In the latter case the changes in T_3 were indicative of posterior infarction. It follows, therefore, that the presence of auricular fibrillation does not interfere with the correct interpretation of the fourth lead.

Defective Intraventricular Conduction and Bundle Branch Block.—There were 23 patients in this group, 12 of whom were regarded as having delayed intraventricular conduction and 11 of whom showed the more classic electrocardiographic signs of left bundle branch block. Five of the former and 6 of the latter were examined post mortem. One of the patients with delayed intraventricular conduction who came to autopsy and showed anterior infarction had a Q wave of 0.5 mm. in the apical lead and a markedly depressed ST segment. The 4 others had no infarction, and all showed a normal Q wave in the apical lead, although in many of the other precordial leads the Q wave was absent. There were 3 patients for whom the clinical evidence was adequate for the diagnosis of coronary thrombosis, and all showed complete absence of the Q wave in all the precordial leads. The interpretation of the presence or absence of myocardial infarction on the basis of the findings in lead IV was correct in all the cases of delayed intraventricular conduction.

The only difficulty that arose in the interpretation of the apical lead occurred for the group showing left bundle branch block. Of the 6 who were examined post mortem, 3 had anterior myocardial infarction, 1 of whom also had posterior infarction. In the last instance a Q wave, 14 mm. deep, was obtained with the apical lead. It has been suggested [4] that the combination of anterior and posterior infarction may explain the presence of the Q wave in cases such as this. In the other 2 instances

of a proved anterior lesion, a Q wave with the apical lead was absent in 1 case and was 2 mm. deep in the other. The 3 who showed no infarction had Q waves with the apical lead of 2, 3 and 4.5 mm., respectively. Of the 5 remaining patients with bundle branch block, 3 had clinical evidence of coronary thrombosis. One of these had a Q wave of 1 mm., another had a Q wave of 0.5 mm. and the third had an M shaped complex extending 7 mm. upward and downward. The last 2 patients had no clinical evidence of myocardial infarction and showed Q waves of 2 and 6 mm., respectively. The direction of the T wave shown by the group of patients with either delayed intraventricular conduction or bundle branch block was of no diagnostic aid, as it was found to be upright or inverted whether infarction was present or not. As a result of this analysis it may be stated that with occasional exceptions the same method of interpreting the apical lead applies when there is bundle branch block or normal intraventricular conduction.

COMMENT

Since the precordial lead first came into use there has been great variation in the technic employed by different investigators and in the opinions as to what position over the precordium gives the most useful findings. The technic originally described by Wolferth and Wood [2] was the use of the indifferent electrode in the interscapular region and the exploring electrode over the midprecordium. Since that time numerous reports have shown that it matters little where the indifferent electrode is placed, whether in the interscapular position or on the left leg. There has, however, been considerable disagreement as to the point of application of the exploring electrode. Some investigators have used two points for the exploring electrode—the left sternal border in the fourth interspace and the apex.[5] Others have used several points of application for the exploring electrode.[6] It now seems to be the consensus that the optimum point from which the chest lead should be taken is the apical impulse. Our results are in complete accord with this view. Bohning and Katz,[7] however, stated that the left sternal border in the fourth

5. (*a*) Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of Chest Leads, Arch. Int. Med. **52**:752 (Nov.) 1933. (*b*) Levine, H. D., and Levine, S. A.: An Electrocardiographic Study of Lead IV with Special Reference to the Findings in Angina Pectoris, Am. J. M. Sc. **191**:98, 1936. (*c*) Wolferth and Wood.[2]

6. Hoffman, A. M., and Delong, E.: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage, Arch. Int. Med. **51**:947 (June) 1933. Master, Dack, Kalter and Jaffe.[4]

7. Bohning, A., and Katz, L. N.: Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion, Arch. Int. Med. **61**:241 (Feb.) 1938.

interspace is the best place to apply the electrode. They held this view because of the difficulty in finding the apical impulse in some cases. In this study the left sternal position in the fourth interspace was much less reliable than either the apex or the fifth interspace in the midclavicular line. In numerous instances patients without cardiac infarction at autopsy had no Q wave when the electrode was at the left fourth interspace and had a normal Q wave when it was at the apex. We believe that if the apical impulse cannot be definitely localized, the next most reliable information will be obtained by placing the electrode at the midclavicular line in the left fifth interspace. In our experience this position was unreliable in cases in which the heart was large and in which the apical impulse was easily located. In this regard, Master, Dack, Kalter and Jaffe [4] observed 3 patients with enlargement of the heart without myocardial infarction who had no Q wave in the precordial lead. The precordial position used by them was just inside the apical impulse. We have studied 5 similar cases in which there was no Q wave with any precordial position except directly over the apical impulse. Each patient had a Q wave of 2 mm. or more with this position. All were examined at autopsy and had no myocardial infarction. It is suggested from this study that the exceptions recorded in the literature may be less frequent in the future if the electrode is placed over instead of inside the apical impulse.

Master, Jaffe and Dack [8] have also reported transient episodes in which the Q wave was absent during the course of acute glomerulonephritis, explained on the basis of diffuse capillary damage of the myocardium. As the process recedes the Q wave reappears. No studies were made of patients with acute nephritis in this investigation.

The significance of an upright T wave with the apical lead has been a point of controversy. Wolferth and Wood [2] said they considered this finding as indicative of coronary occlusion. Wood and his colleagues,[5a] Shipley and Hallaran [9] and Sorsky and Wood,[10] in studying large groups of normal persons, found no upright T wave with the apical lead. Master [11] and Edeiken, Wolferth and Wood [12] noted an upright T wave

8. Master, A. M.; Jaffe, H. L., and Dack, S.: The Electrocardiogram in Acute Nephritis, Am. Heart J. **12**:244, 1936.

9. Shipley, R. A., and Hallaran, W. R.: The Fourth-Lead Electrocardiogram in Two Hundred Normal Men and Women, Am. Heart J. **11**:325, 1936.

10. Sorsky, E., and Wood, P.: The Use of Chest Leads in Clinical Electrocardiography, Am. Heart J. **13**:183, 1937.

11. Master, A. M.: The Precordial Lead in One Hundred and Four Normal Adults, Am. Heart J. **9**:511, 1934.

12. Edeiken, J.; Wolferth, C. C., and Wood, F. C.: The Significance of an Upright or Diphasic T-Wave in Lead IV When It Is the Only Definite Abnormality in the Adult Electrocardiogram, Am. Heart J. **12**:666, 1936.

with the apical lead only rarely when cardiac infarction was not present. These investigators said they considered the presence of an upright T wave as definitely abnormal. Of this series of 75 persons with normal hearts, 4 showed an upright T wave with the apical lead. Three of these were proved to have normal hearts at autopsy. Of the 43 patients who had pathologic hearts without myocardial infarction, 12 showed an upright T wave with the apical lead. Nine of these came to autopsy and had no evidence of cardiac infarction. An upright T wave with the apical lead therefore occurs rarely when the heart is normal and not infrequently when the heart is pathologic without myocardial infarction. Other peculiarities in the form of the T wave with lead IV have been commented on. For instance, Katz and Kissin [13] stated that a T wave more than 9 mm. deep should be regarded as abnormal. Sorsky and Wood [10] said they considered the deep T wave as normal. We have observed T waves as deep as 15 mm. when the heart was normal (table 1). Digitalis has been shown by Strauss and Katz [14] and Stewart and Watson [15] to produce variable changes in the ST segment and T wave in lead IV. From this discussion it is obvious that there are several conditions that may alter the form of T_4 and that there is no general accord among investigators as to the significance of these variations. It is clear that a good deal of work must be carried out with respect to the conditions under which alterations of T_4 can occur. It is only in this way that the diagnosis of myocardial infarction can be further clarified.

SUMMARY

A study was made to ascertain which point over the precordium could be used in taking the so-called lead IV that would furnish the most reliable information in the diagnosis of myocardial infarction. For this purpose 9 or 10 tracings were taken with the electrode in various parts of the precordium in each of 352 cases. The two main criteria that were analyzed were the presence or absence of the Q wave and the direction of the T wave. In this study tracings were regarded as indicative of myocardial infarction if the Q wave was absent. They were called questionably indicative of infarction if the Q wave was less than 2 mm. deep. The term abnormal was used when a normal Q wave was present but the T wave was upright. It was found that interpretations of the

13. Katz, L. N., and Kissin, M.: A Study of Lead IV: Its Appearance Normally in Myocardial Disease, and in Recent Coronary Occlusion, Am. Heart J. **8**:595, 1933.

14. Strauss, H., and Katz, L. N.: Effect of Digitalis on the Appearance of Lead IV, Am. Heart J. **10**:546, 1935.

15. Stewart, H. J., and Watson, R. F.: The Effect of Digitalis on the Form of the Human Electrocardiogram, with Special Reference to Changes Ocurring in the Chest Lead, Am. Heart J. **15**:604, 1938.

electrocardiograms obtained with the electrode over the base of the heart and along the sternum were often misleading. The error decreased as the apical region was approached. It was also found that the electrocardiograms obtained with the electrode in the region of the nipple or in the midclavicular line, although generally reliable, were frequently not so when there was considerable cardiac hypertrophy. The only lead that gave a curve for which a satisfactory interpretation could be made with an extreme degree of accuracy was the one for which the electrode was placed over the apical impulse of the heart.

For 75 persons with normal hearts the Q wave was normally present and deepest with the apical lead. With the other positions it was often small (less than 2 mm.) and rarely absent. The T wave was frequently upright with many of the precordial positions and in 4 instances even with the apical lead.

Deep inspiration was found to shorten the Q wave and to change an inverted to an upright T wave in some instances. More reliable information could be obtained during normal breathing than during deep inspiration.

Although minor differences in the electrocardiograms were noted with the patient in the supine, upright, left lateral or right lateral position, these did not alter the accuracy of the interpretations with the apical lead.

It was found that when fluid was present in the left pleural cavity, an absent or small Q wave might become normal after thoracentesis. The removal of fluid from the abdomen changed a small Q wave to a normal one.

When the heart was considerably enlarged, owing to vascular disease, hypertension or other causes, frequently there was no Q wave with any of the precordial leads except the apical. The T wave was often upright even with the apical lead.

Two patients with syphilitic narrowing of the coronary ostia without myocardial infarction showed a Q wave of only 0.5 mm. with the apical lead.

The presence of auricular fibrillation or delayed intraventricular conduction did not interfere with the correct interpretation of the fourth lead. In 2 of the 11 cases of left bundle branch block the method of interpretation of lead IV used in this study was incorrect.

It can be concluded that, except in the rare instances cited, a Q wave of 2 mm. or more in the electrocardiogram with the apical position will always be found when the heart is normal or when there are various forms of heart disease unassociated with anterior myocardial infarction.

THE PRECORDIAL LEAD

II. FINDINGS FOR PATIENTS WITH MYOCARDIAL INFARCTION

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In the preceding paper [1] the use of multiple points over the precordium in obtaining lead IV was discussed. In that paper the findings for patients with normal hearts and for those with various pathologic conditions of the heart and lungs other than myocardial infarction were reported.

A similar study has been made of patients suffering from, or suspected of having, myocardial infarction. The technic was the same as that used in our previous study; i. e., nine designated points over the precordium were employed (see figure 1 in the first paper). If the apex was outside the ninth position an additional tracing was made with the electrode placed directly over the apex of the heart. The positions will be referred to in the future as leads IV_1, IV_2, IV_3, etc. The customary German silver electrodes (1½ by 2 inches [3.8 by 5 cm.]) were used. The exploring electrode was placed over the precordium with its long axis parallel to the long axis of the body. The indifferent electrode was placed on the left leg; the right arm electrode was used as the exploring electrode.[2] The normal tracing obtained by this method consists of an initial downward deflection of more than 2 mm. (Q wave) and an upward R deflection and an inverted T wave. A tracing which has a normal Q wave of 2 mm. or more but an upright T wave is considered as abnormal, the presence of a Q wave of less than 2 mm. as questionably indicative of myocardial infarction and absence of the

Submitted for publication, July 16, 1938.
From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Robinson, R. W.; Contratto, A. W., and Levine, S. A.: The Precordial Lead: I. Findings for Patients with Normal Hearts and Those with Heart Disease Other Than Myocardial Infarction, Arch. Int. Med., this issue, p. 711.

2. Since this study was completed it has become the custom to reverse the polarity in making lead IV, so that the reader will need to look on these curves as opposite to those that are now being obtained (mirror image).

Q wave as positive evidence of myocardial infarction. Likewise a marked deviation of the ST segment from the isoelectric line is considered indicative of the acute stage of myocardial infarction.

MATERIAL

Tracings were taken for 82 patients who had typical histories and clinical findings of cardiac infarction or who showed changes in the conventional leads which could be interpreted as indicative of cardiac infarction. In 20 of these cases myocardial infarction was proved at autopsy. Fifty-three of the patients were men, whose ages varied from 31 to 81 years, with an average age of 52.2; and 29 were women, the youngest being 48 and the oldest 87, with an average age of 64. In careful analysis of the tracings no significant differences were noted between those for men and those for women; therefore, no further detailed differentiation of the two sexes will be made. Studies were also conducted on a group of patients who had histories suggestive of coronary thrombosis.

During this study we had the opportunity of making tracings for several different groups of patients. Twenty-eight of the patients, as far as could be determined, were suffering from a first attack of cardiac infarction. The infarction was of the anterior type, and tracings were obtained within the first week of illness. Sixteen additional patients were judged to have had only one healed myocardial infarction. Electrocardiographic changes showed it to be of the anterior type, and the history suggested that it was at least six weeks old. The time which elapsed between the acute episode and the making of the tracing varied from six weeks to twenty-five years. The average interval was sixteen months, not including one unusual interval of twenty-five years. Seven patients had acute myocardial infarction of the posterior type. Thirty had multiple cardiac infarcts, and for 14 the diagnosis was verified at autopsy. Some cases were also included in which the history, clinical findings and electrocardiographic tracings were suggestive but not typical of cardiac infarction.

ACUTE ANTERIOR INFARCTION

For 28 patients who were suffering from acute anterior infarction, conventional electrocardiograms were made, together with tracings from the nine previously designated points over the precordium and from the apex of the heart if it was outside the position indicated. Tracings were obtained for the majority of these patients within a day or two after the acute episode, and all had tracings taken within the first week of illness.

For 6 of the 28 patients the first electrocardiograms showed no diagnostic evidence of cardiac infarction in the three conventional leads, while the tracings taken from the precordium were typical. Subsequent conventional leads, however, showed changes in 3 cases which were typical of acute anterior infarction.

The Q Wave.—From the majority of these first precordial electrocardiograms the Q wave was absent. However, it may not disappear for several hours or days after the acute episode. In 1 of our cases in which

the clinical history and findings were typical of cardiac infarction and in which changes in the electrocardiograms were indicative of acute anterior infarction, there was a Q wave of 2.5 mm. until the seventh day, when it was 1.5 mm., and it did not disappear entirely until fifteen days after the acute attack (fig. 1). Another patient retained a small Q wave until the twenty-eighth day after the acute episode, when it disappeared. It seems, therefore, that although a Q wave is not found in the apical lead in most cases of anterior infarction, it may not disappear for a few weeks after the onset of the acute attack.

Electrocardiographic tracings taken from the nine positions over the precordium and from the apex showed no Q wave in the majority of these cases of acute cardiac infarction of the anterior type. In several cases a small Q wave, of less than 1.5 mm., was present with the first to ninth positions and absent with the apical position. In the occasional case a Q wave of less than 1 mm. was present also in the apical lead. One patient, who showed clinically typical symptoms of acute myocardial infarction and at autopsy showed a recent large infarction of the anterior portion of the myocardium, had normal conventional leads and also a deep Q wave in the tracings taken from all the nine points over the precordium except the one taken from over the apex, which showed no Q wave (fig. 2). In this case the apical lead was the only one from which a decisive electrocardiographic diagnosis could be made. Two other patients who had clinical coronary thrombosis and who also showed progressive changes in the conventional leads showed absence of the Q wave only in the eighth, ninth and apical leads. On the other hand, occasionally the conventional leads may be characteristic of anterior infarction when all the precordial leads are normal (fig. 3).

In several cases tracings were taken from a point 3 cm. outside the apical impulse. The majority of these tracings were of the same general type as those obtained elsewhere over the precordium. However, in some the Q wave, which was absent with the apical position, was prominent with the lead taken 3 cm. lateral to the apex (fig. 4). It follows that in the majority of cases of acute anterior infarction, tracings taken from any point over the precordium show no Q wave. In some cases a Q wave was absent only from the apical lead. Tracings taken to the left of the apical impulse were unreliable. This is further evidence of the reliability of the apical position in obtaining lead IV.

The ST Segment in Acute Anterior Infarction.—Wolferth and Wood,[3] in their original article on lead IV, called attention to the depression of the ST segment in cases of acute cardiac infarction. In

3. Wolferth, C. C., and Wood, F. C.: Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, Am. J. M. Sc. **183**:30, 1932.

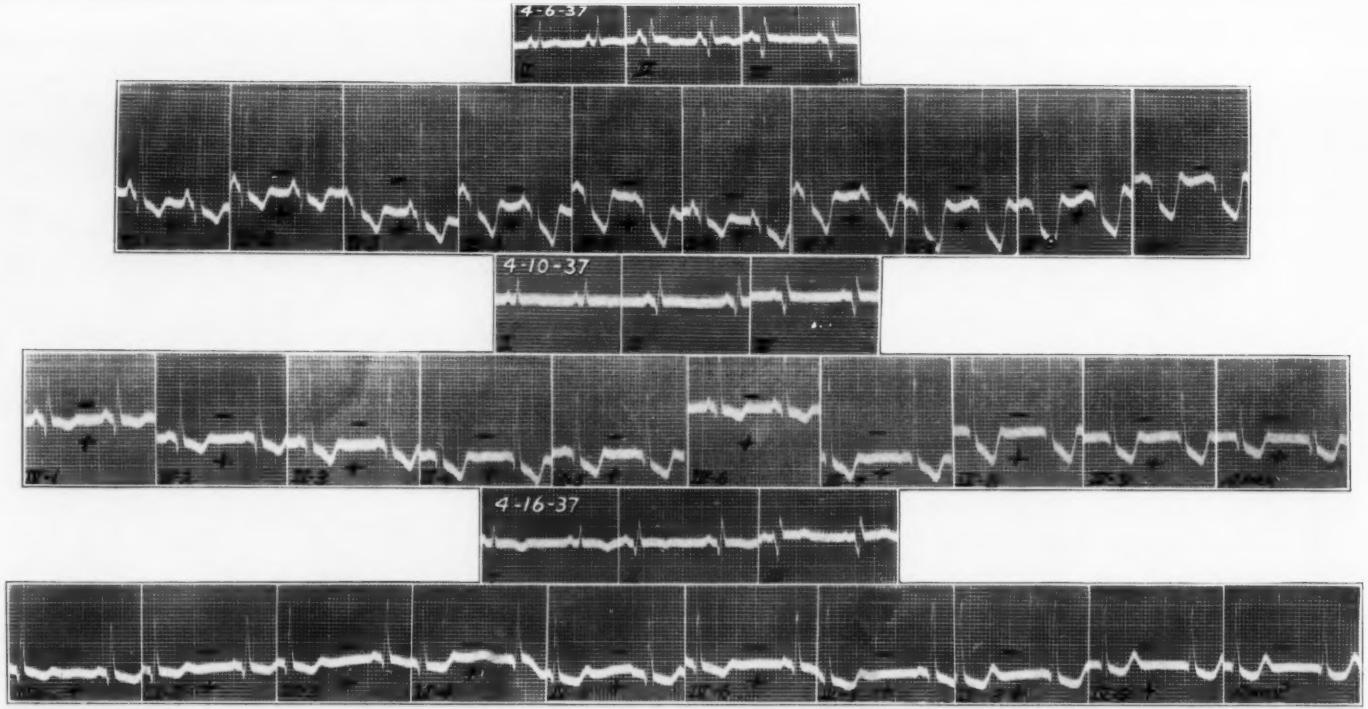

Fig. 1.—Note the progressive changes in the conventional leads. The tracings were made three, nine and thirteen days, respectively, after the acute attack. Note also the deeper ST segment and more marked changes in the apical leads than in other precordial leads and the progressive shortening of the Q wave in the apical leads.

the majority of cases of acute anterior infarction, depression of more than 3 mm. of the ST segment is regarded as one of the most pathognomonic findings in tracings taken from the precordium. Rarely in the early hours or days after an acute infarction it may be the only positive electrocardiographic evidence in the conventional or precordial tracings. In our series 3 patients had as their only early change, depression of the

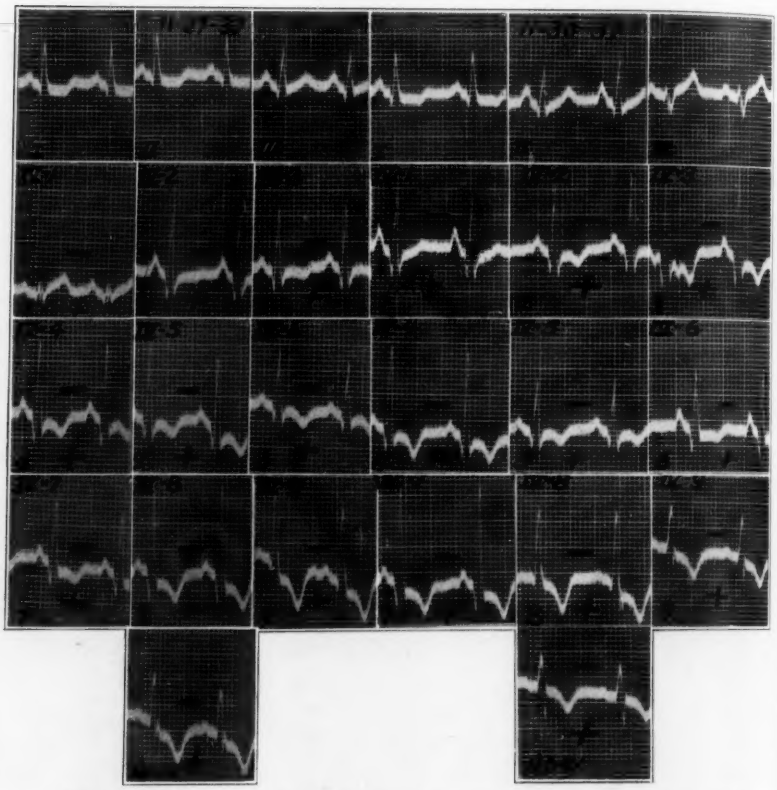

Fig. 2.—Note the absence of the Q wave only in the ninth and the apical lead, which was the only distinctive electrocardiographic evidence of anterior infarction shown in this case. At autopsy there was an acute anterior infarction. The tracings were made on the first and fourth days of illness.

ST segment in the precordial leads. This depression was present in practically all tracings taken from the precordium for every one of the 28 patients in this series. However, it was usually most prominent in tracings obtained from the apical region, in which the average depression

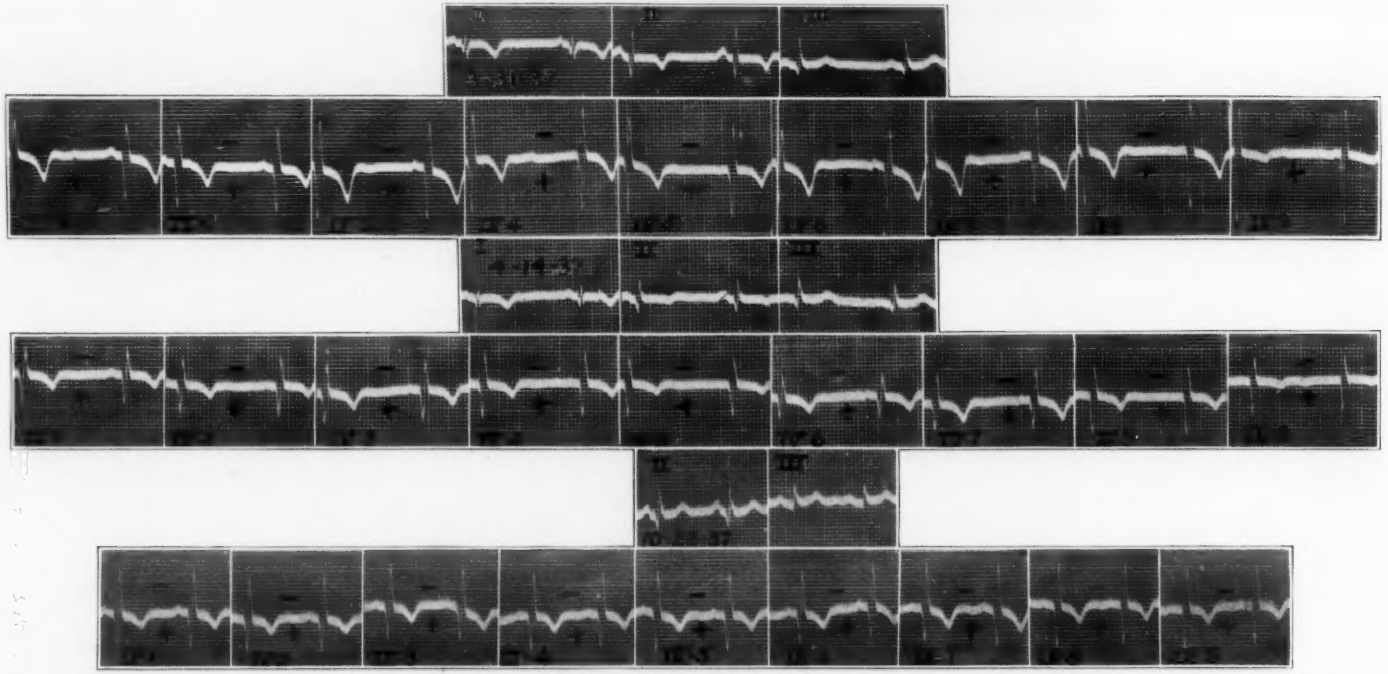

Fig. 3.—A typical attack of coronary thrombosis occurred on March 18, 1937. Note that the conventional leads indicate an anterior infarction, whereas all the precordial leads are normal.

of the ST segment was about 4.3 mm., with extremes of 1.5 to 10 mm. With other positions it averaged as little as 1.8 mm. (table 1).

In serial precordial tracings taken every other day for this group of patients it was noted that the most rapid changes were in the ST segment. It was generally deepest during the first day and gradually

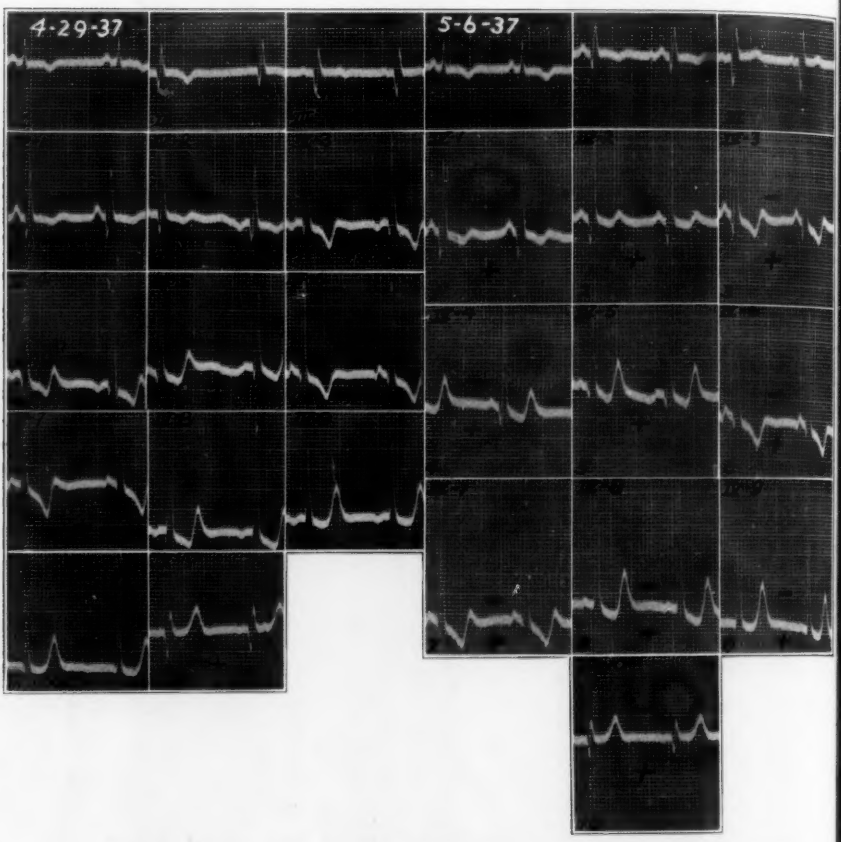

Fig. 4.—Note the absence of a Q wave in the ninth precordial and apical leads, which is indicative of anterior infarction, but the appearance of a large Q wave in the tenth lead, taken 3 cm. outside the apex.

returned to the isoelectric line during the course of seven to fourteen days. The T wave became progressively more upright during this interval. In 1 case this change from a depressed ST segment to an upright T wave took place in as short a time as four days, while in

another it took place twenty days after the acute episode (fig. 5). It was also noted in many cases that this change in the ST segment, with the T wave becoming progressively positive, took place much more rapidly in the tracings taken from the apical region, and no decisive change of the ST segment appeared in tracings from other parts of the precordium made during the six weeks of observation (fig. 6).

One may conclude that if the criterion of a depressed ST segment which progressively changes to an upright T wave is to be used in the diagnosis of acute anterior infarction, as this evidence is more pro-

TABLE 1.—*Depression of the ST Segment in Leads from Various Points Over the Precordium in Cases of Acute Anterior Infarction* *

	Precordial Position									
Patient	1	2	3	4	5	6	7	8	9	Apex
1.....	0	1	0.5	1.5	2	0	0.5	2.5	2.5	1.5
2.....	1.5	2.5	1.5	2.5	2.5	1.5	1.5	2.5	2.5	2
3.....	0	0	0.5	2.5	2.5	1.5	0.5	2	2.5	3
4.....	0.5	0.5	1	1.5	2	0.5	1.5	2.5	2	2
5.....	2	2	0.7	2.5	2	1.5	1.5	1.5	2.5	2.5
6.....	0	1	5	1.5	2	0	0.5	2.5	2.5	1.5
7.....	0	0	0.5	2.5	2.5	1.5	0.5	2	2.5	3
8.....	2	2	0.7	2.5	2	1.5	1.5	1.5	2.5	2.5
9.....	1	1	1	1	1	1	2	6	8	8
10.....	1	2	2	3	4	2	2.5	5	4.5	5
11.....	1	1	0	1	1.5	1.5	1.5	2	2	2
12.....	0.5	1	2	1.5	2	2	3	2.5	2	2
13.....	0	0	0	0	0	0	0	2	3	3
14.....	3	2.5	2.5	4	3	2	3.5	4	3.5	3.5
15.....	5	5	4.5	5	5	2	5	5	7.5	6
16.....	2	2	2	3	4	2	8	12	9	9
17.....	2	3	4	6	6	3	4	5.5	6	6
18.....	0	2	3	4	4	2	3	5	6	5
19.....	0	0	3	4	5	0	3	5	6	6
20.....	4	3	0	4	4	2	2	4	4	4
21.....	1	1	1	2.5	2.5	0.5	2	2.5	3	3
22.....	2	3	5	5	5	0	2.5	4	4	4
23.....	7	8	7	10	10	5	6	8	9	10
24.....	5	5	4.5	5	5	2	5	5	7	6
25.....	0	0	0	0	0	0	0	2	3	3
26.....	0.5	1	2	1.5	2	2	5	2.5	2	2
27.....	1	2	2	3	4	2	2.5	5	4.5	5
28.....	1	1	1	1	1	1	2	6	8	8
Average	1.5	1.8	2	2.9	3	1.4	2.5	3.5	4.3	3.9

* The measurements are given in millimeters.

nounced in tracings taken from over the apex than in those from other points in the precordium, the apical region is the optimal position from which the fourth lead should be taken.

PATIENTS WITH ONLY ONE INFARCT OF SIX WEEKS' OR MORE DURATION

Tracings were taken for 16 patients who, as far as could be determined from the history, clinical findings and electrocardiograms, had had only one previous cardiac infarction, which was at least six weeks old. The interval between the occurrence of the infarction and the making of the first electrocardiogram varied from six weeks to twenty-five years.

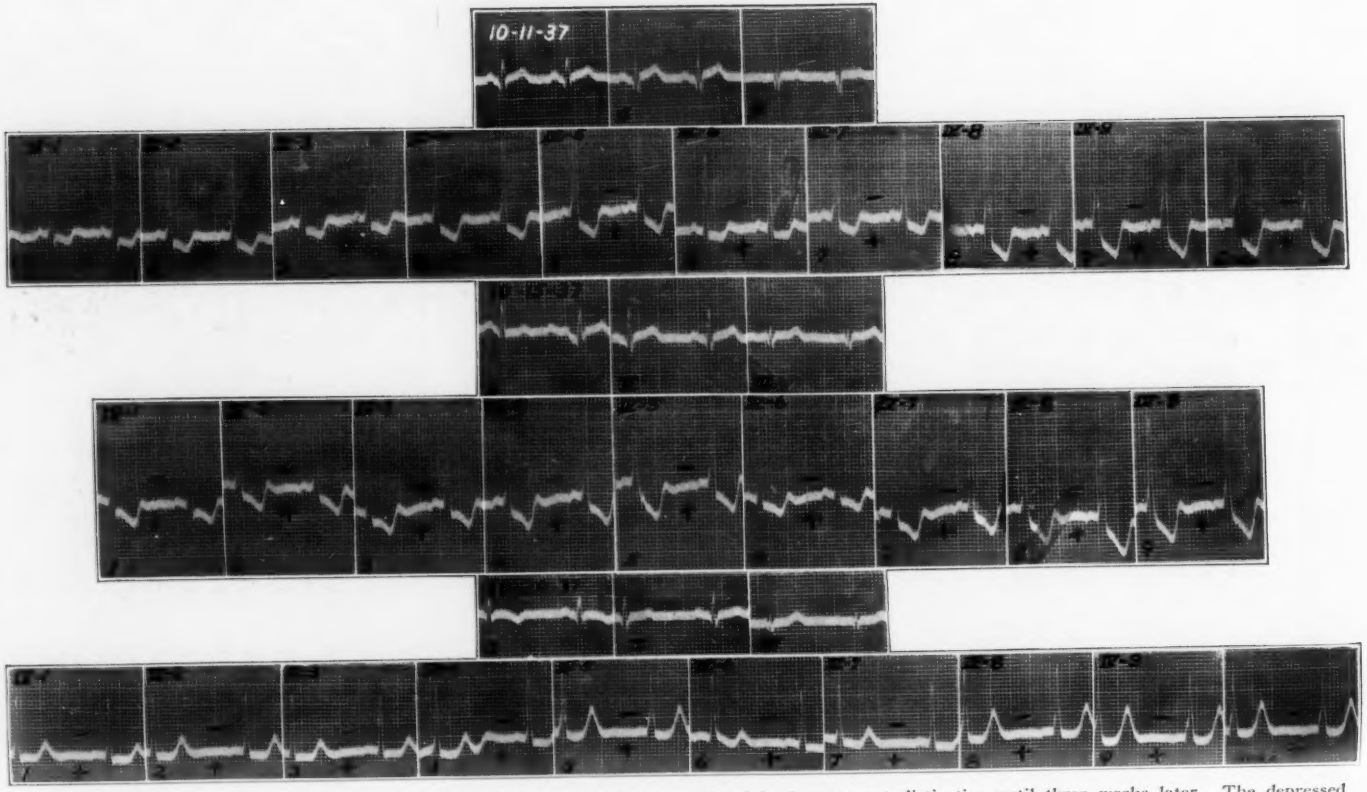

Fig. 5.—The acute attack occurred on Oct. 9, 1937. Note that the conventional leads were not distinctive until three weeks later. The depressed ST segment in the precordial leads, especially in the apical lead, ending in an upright T wave, was fairly indicative of the diagnosis.

ST segment in the precordial leads, especially in the apical lead, ending in an upright T wave, was fairly indicative of the diagnosis.

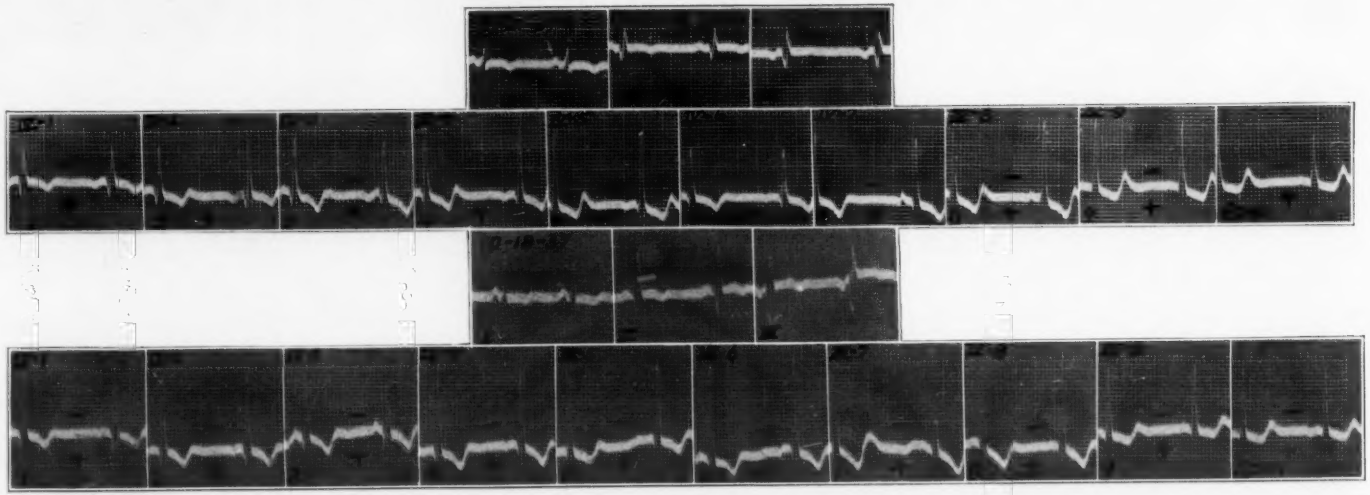

Fig. 6.—The acute attack occurred on April 5, 1937. Note that there was an upright T wave only in the ninth and apical leads.

The average interval, not including the unusual period of twenty-five years, was five and seven-tenths months.

For 9 of these patients the conventional tracings were normal except for left axis deviation in 2 instances. In the conventional tracings for the remaining 7 patients, evidence of distinct myocardial pathologic involvement was present. Tracings taken from the apical region showed no Q wave in any instance, while curves from other parts of the precordium showed a small Q wave, from 1.2 to 2 mm. in several cases. In 10 cases the T wave was upright in the apical lead, varying from 0.5 to 9 mm., with an average of 4.5 mm. In 3 cases the T wave was inverted in the apical lead, ranging from 2 to 3 mm.; and in 2 the T wave was isoelectric (table 2).

In the study of this group it was noted that in no case was a Q wave present in tracings taken from the apical position, while the T wave was upright in only two thirds of the cases. It follows that in the electrocardiographic diagnosis of cases of old single anterior myocardial infarction, the absence of the Q wave in the apical lead is more reliable than the presence of an upright T wave. It also adds further proof to the fact that when there are healed anterior infarcts the only positive electrocardiographic evidence in many cases may be obtained from the fourth lead.

PATIENTS WITH MULTIPLE INFARCTIONS

This group comprised 30 patients, many of whom, we were certain from clinical evidence, had had multiple infarctions. Others had had severe angina with more than one questionable infarction at some time during their illness. Still others showed evidence of multiple infarctions at autopsy.

The tracings for this series of patients were the most difficult to interpret. There were 4 cases in which the Q wave was rare in the various precordial leads except the apical, in which the main deflection was downward. Two of these patients came to autopsy; 1 had an acute posterior infarction (and a suggestive old anterior infarction), and the other had multiple old and recent infarctions of both the anterior and the posterior type. The conventional leads in the first case showed auricular flutter. In the other, bundle branch block was present. The 2 remaining patients were not examined post mortem. One had severe angina for ten years and several attacks suggestive of cardiac infarction. The conventional leads in this case were suggestive of an old infarction (fig. 7). The other patient also had severe angina and showed typical clinical evidence of cardiac infarction. Our experience in these 4 cases in which the entire initial ventricular deflection was downward with the apical lead, although with most of the other precordial positions there was no Q

TABLE 2.—*Tracings Taken from the Various Precordial Positions for Patients with Anterior Infarction of Six Weeks or More*

Patient	Information Obtained from Conventional Leads	Q Wave (Lead IV), Mm.										ST Segment Depressed, Mm.										T Wave, Mm.*										Time Since Acute Episode
		1	2	3	4	5	6	7	8	9	Apex	1	2	3	4	5	6	7	8	9	Apex	1	2	3	4	5	6	7	8	9	Apex	
1	Positive	0	0	0	0	0	0	0	0	0	0	2	3	2	3	3	1.5	2	2.5	2.5	3	u2	u3	u3	u4	u4.5	u2	u2.5	u4.5	u5	u7	6 wk.
2	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u3	u3	u3	u3	u3	u2	u3	u4.5	u4.5	u5	2 mo.
3	Positive	0	0	0	0	0	0	0	0	0	0	0	1	2	2	3	3	2.5	3.5	3.5	0	u2	u5	u6	u6	u7	u5	u5	u7	u8.5	u6	4 mo.
4	Positive	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0	1	1	1	1	1	1	1	2	1.5	1.5	du	du	du	du	du	du	du	du	du	u5	3 mo.
5	Positive	4.5	3	0.5	0	2	1.5	0	0	0	0	0	0	0	0.5	1	0	0	2	3	3	u1	u4	u1	u5	u6	0	u1	u5	u5.5	u9	5 mo.
6	Positive	0	0	0	0	0	0	0	0	0	0	1	1	2	3	3	3	3	3	2	2	u3	u3	u2	u5	u4	u4	u4.5	u5	u4.5	u5	15 mo.
7	Negative	3	2.5	2	1.5	1	1.5	1	0.5	0	0	0	0	0	0	0	0	0	1	2	2	0	0	0	u5	u5	0	u1.5	u2	u2.5	u3	2 mo.
8	Positive	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u5	u6	u5.5	u6	u5.5	u5	u5	u6	u9	u9	8 mo.
9	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u4	u5	u4	u8	u7	u2	u4	u8	u7	u7	6 wk.
10	Negative	1	1	1	1	0.5	1.5	1.5	0.5	0.5	0	1.5	2	0	2	2	1	2	3	3	2.5	d2	d3	d4	d2	d1.5	d4	d4	d2	d2	d3	2 mo.
11	Negative	0.5	1	1	1.5	1.5	2	2	2	0.5	0	0	0	0	0	0	0	0	0	0	0	u2	u3	u2	u2.5	u3	u3	u2	u3	u3	u3	4 mo.
12	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u1.5	u1.5	u2	u1	0	u1	du	0	0	0	5 mo.
13	Negative	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	2	1	2	2	d1	d1.5	d1	d1.5	d5	d2	d3	d3	d3	d3	2 yr.
14	Positive	..	..	..	..	..	..	..	..	..	0	..	..	..	..	..	..	..	..	..	0	...	...	...	...	...	...	...	...	...	du	25 yr.†
15	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	d1	u2	u2	du	du	du	d1.5	d3	d2	d2	4 yr.
16	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u3	u2.5	u2.5	u1.5	u5	u1.5	u1.5	du	0	0	3 yr.

* u indicates upright; d, inverted; du, diphasic; 0, isoelectric.

† Only apical tracings were obtained.

wave, suggests that when such a downward wave is found with the apical lead, multiple leads should be taken from other parts of the precordium. When most of these do not show a Q wave, one may regard this as presumptive evidence of myocardial infarction.

We had the opportunity of obtaining tracings for 2 patients who were observed during the acute stage of two separate attacks of coronary

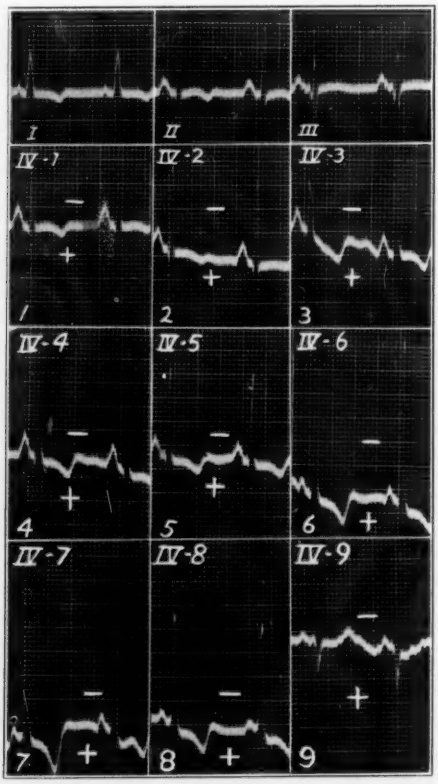

Fig. 7.—The patient had had severe angina for ten years. The electrocardiograms were suggestive of infarction nine months and three months before these tracings were made. Note that the conventional leads are suggestive; the Q wave is absent from every precordial lead except the apical, where the entire complex is downward.

thrombosis. In the first case the attack of posterior infarction occurred almost ten years after recovery from an anterior infarction (fig. 8). It is interesting that the Q wave with the apical lead was still absent so many

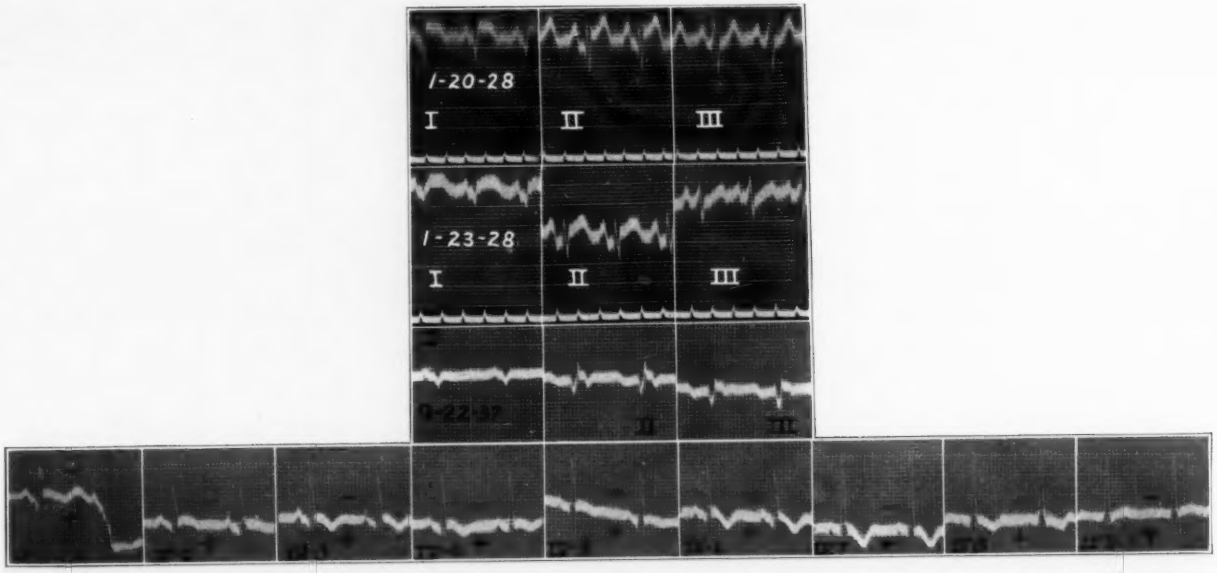

Fig. 8.—An attack occurred on Jan. 19, 1928. The early curves indicated the presence of an anterior infarction. Note that even ten years later there was no Q wave in the apical tracings.

years after the anterior infarction. The evidence of the new posterior lesion was apparent in the three conventional leads. In the second case a typical attack due to anterior infarction occurred, with recovery. This was followed six months later by another attack due to anterior infarction, and at this time the ST interval was again depressed (fig. 9). The first anterior lesion, though healed, did not prevent the appearance of evidence of a fresh similar lesion.

In analyzing the remaining 24 cases we found that the conventional leads were normal in 7 cases; bundle branch block was present in 5; a low electromotive force, in 2; auricular fibrillation, in 2; auricular flutter, in 1; defective intraventricular conduction, in 1, and curves indicative of old anterior infarction, in 6. In none of these cases was there a Q wave of more than 1.5 mm. in tracings taken from the apical position. In 15 instances the Q wave was absent from tracings with all positions over the precordium. In 5 the Q wave was absent only with the apical position, while tracings from other parts of the precordium showed a Q wave of 1 or 2 mm. In 8 cases there was a Q wave of 1 mm. or less with the apical lead and of 2 mm. or less with leads from other points over the precordium. In 2 cases a small Q wave, of 1 mm., was present with the apical lead and was absent with leads from other points over the precordium. Moreover, in none of the cases in which autopsy was performed was there a Q wave of more than 2 mm. in the apical lead, with the exception of the 2 instances previously mentioned in which the entire deflection of the QRS complex was downward. The direction of the T wave was too variable to be of diagnostic aid in these cases of multiple infarctions.

SERIAL TRACINGS FOR PATIENTS WITH ACUTE ANTERIOR INFARCTION

Tracings were taken for 17 patients with acute anterior infarction every two or three days for a period of four to five weeks, and for some the tracings were taken six weeks to two years after the acute attack. No patient, as far as is known, had an attack of coronary thrombosis in the interim.

For 10 of this group the conventional leads were characteristic of acute anterior infarction at the time the original electrocardiograms were taken. In 3 cases the conventional leads were suggestive, and in 3 they were normal. Subsequent conventional leads for those with suggestive tracings showed definitely positive evidence in three to six days. In only 2 cases did the conventional leads return to normal while the patient was under observation (seven and sixteen months, respectively) after they had shown definitely positive evidence. In 2 cases the curves became suggestive but not definitely indicative of coronary thrombosis. In 3 instances in which the conventional leads were suggestive, these leads

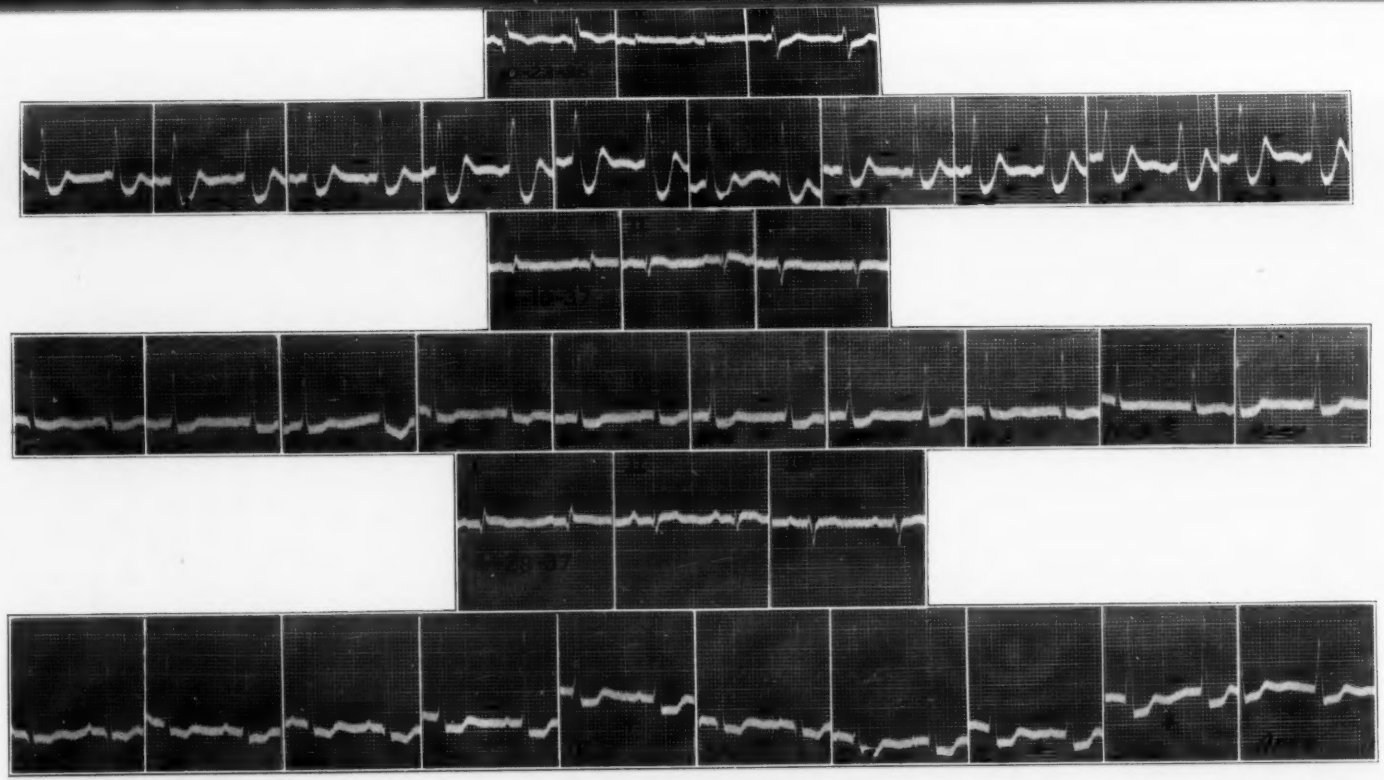

Fig. 9.—The first attack occurred on Oct. 20, 1936. Conventional and precordial leads were made on October 23; all were typical of acute anterior infarction. Tracings were made on April 10, 1937, while the patient was having anginal attacks; note the residual evidence (absent Q_1) of an old anterior lesion. A second attack of thrombosis occurred on April 24, 1937. Note that four days later the RT segment was noticeably depressed in the apical lead.

reverted to normal in one to two months. Subsequent electrocardiograms taken for these patients twenty-one months after the acute stage still showed normal conventional tracings.

The Precordial Q Wave.—In 1 case the Q wave remained normal throughout the period of observation (fig. 3). For the remaining group it was absent with the apical position in every case. With some of the other positions a small Q wave, of less than 2 mm., was present in some instances. In the serial follow-up tracings for these patients, the Q wave remained absent in 14 cases, while in 2 it returned to a depth of 0.5 and 1 mm., respectively. In another case it returned to a depth of 2 mm. in the apical lead. At autopsy this patient had an old left anterior descending and an acute posterior thrombosis. This is the only case in which the Q wave returned to an extent which would be considered normal in the apical lead, although a more prominent Q wave reappeared with other positions over the precordium.

The Precordial T Wave.—In serial tracings the T wave became upright during the acute stage in 11 of the 17 cases. This change, as previously mentioned, occurred most rapidly in the apical lead. In the majority of instances the T wave reached its greatest upward deflection on about the tenth to the fourteenth day after the acute episode and then receded to a fixed point, but it remained upright to a certain degree during the period of observation. In 8 of these cases it remained upright for periods up to two years. However, in 3 cases it went through the progressive changes from a depressed ST segment to an upright T wave and during the period of observation became inverted again. In 6 cases the T wave never was upright during the period of observation.

Comment.—It follows that the most constant change in the precordial leads for this group of patients was the absence of the Q wave from tracings taken from the apical region. Likewise, in serial tracings the Q wave did not return to a size of more than 2 mm. in any case while the patient was under observation. In contrast, the changes in the T wave were variable and less reliable.

ACUTE POSTERIOR MYOCARDIAL INFARCTION

In our experience acute posterior infarction was much less common than acute anterior infarction. It was encountered in only 7 instances during this study. For this group the conventional tracings were positive in every case; i. e., the take-off was low in lead I and high in lead III. In no instance was information obtained from the precordial tracings which was not in evidence in the first three leads. In fact, in 3 of these cases there was no change in the precordial tracings other than a deep Q wave. This finding was encountered frequently in our study of persons with normal hearts.[1] In several instances a high take-off of the

ST segment was present in the precordial tracings only with the apical lead, and this change was more transient in the precordial tracings than in the conventional lead III (table 1). We did not find the precordial tracings of any additional value in cases of acute myocardial infarction of the posterior type.

THE SIGNIFICANCE OF AN UPRIGHT T WAVE AS THE ONLY ABNORMALITY IN THE PRECORDIAL ELECTROCARDIOGRAM

In a previous publication it was shown that the T wave was more frequently upright than inverted in tracings taken from certain positions over the precordium. This finding, however, was less frequent with the apical position than with other positions over the precordium. We did find an upright T wave rarely when the heart was absolutely normal and frequently when there was a diseased heart without myocardial infarction.[1]

In the combined review of cases in this and our previous study[1] an upright T wave in the apical lead as the only abnormality of lead IV was found in 47 instances. Two of these patients were healthy young nurses with normal hearts, and 2 were young persons who died of a disease entirely unrelated to the cardiovascular system and whose hearts were normal on postmortem examination. Two were elderly patients who died of carcinomatosis and whose hearts were normal post mortem. Of the remaining, 8 had hypertension and uremia, 2 of whom showed no infarctions at autopsy; 8 had hypertension with cardiac failure, 2 showing no infarction at autopsy. Eight had angina, 4 with and 4 without hypertension, none of the patients being examined post mortem. Five had valvular heart disease, and the 1 examined post mortem had no cardiac infarction. Four had syphilitic aortitis, 2 of whom showed no infarction at autopsy. One had bronchopneumonia without obvious heart disease, and 1 had carcinoma of the left lung and a normal heart (verified at autopsy). There were only 4 patients in this group who had evidence suggestive of coronary thrombosis, none of whom were studied post mortem. One of these had syphilitic aortitis, and 2 were in the group previously discussed with absence of the Q wave in every lead except the apical, where the entire complex was downward. The remaining patient had several bouts of severe precordial pain without fever or leukocytosis.

It follows that an upright T wave as the only abnormality in lead IV was frequently encountered. However, in the great majority of instances it was not due to cardiac infarction. In fact, during this study we did not encounter a single case in which there was indisputable clinical evidence of coronary thrombosis or in which cardiac infarction was present post mortem in which an upright T wave in the precordial lead was the only abnormality.

COMMENT

The recent introduction of precordial leads in clinical electrocardiography has opened up a new method of cardiac diagnosis. So far its practical application has been essentially confined to the diagnosis of myocardial infarction. When electrocardiographic studies were limited to the three conventional leads the technic was simple and standard, so that all data were readily comparable. Now one is faced with a method which gives results that vary greatly, depending on which point over the precordium is explored. The obvious aim is to derive all the useful information in as simple a manner as possible.

This study was undertaken to determine which single point over the precordium affords the most trustworthy information and to discover how often that single point will prove inadequate. We have presented data to show that a tracing obtained with the exploring electrode over the apex of the heart and the indifferent electrode on the left leg furnishes more reliable information than does a tracing from any other single point but that occasionally it may fail to disclose important alterations in the electrocardiogram which could be obtained by the study of multiple precordial leads. In general, this confirms the judgment of F. N. Wilson,[4] who stated that "the information obtained from a single precordial lead is likely to prove misleading, but if, to save time, one lead is taken it is probably best to place the exploring electrode upon the apex beat or in its immediate neighborhood." Just as he has mentioned, we have found a few instances in which absence of the Q wave from a tracing taken with the electrode near the sternum afforded positive evidence of myocardial infarction when the tracings obtained from the apical region did not. It is hoped that with further studies, such as those of Kossman and de la Chapelle,[5] on the part of various investigators general rules will be established regarding the indications furnished by the use of multiple leads, so that for routine practice only the apical position will be necessary but that under specific circumstances other leads will need to be used.

SUMMARY

For 82 patients who had typical histories and clinical findings of myocardial infarction an electrocardiographic study was made using three conventional leads and nine additional chest leads from over the

4. Wilson, F. N., in Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936, p. 281.

5. Kossman, C. E., and de la Chapelle, C. E.: The Precordial Electrocardiogram in Myocardial Infarction: Observations on Cases with Infarction Principally of the Anterior Wall of the Left Ventricle and the Adjacent Septum, Am. Heart J. **15**:700, 1938.

precordium. The main purpose was to ascertain which single point affords the most reliable diagnostic data.

Absence of a Q wave [2] from the precordial curves obtained from the apex was the most constant and reliable indication of anterior myocardial infarction. In a few instances, several days to four weeks elapsed after the acute attack before the Q wave disappeared. In 1 case of anterior infarction a normal Q wave persisted indefinitely. When the Q wave did disappear from the apical lead, it was not found to return on follow-up study.

The direction of the T wave, though generally upright, was not found to have reliable diagnostic value.

A significant deviation of the ST segment from the isoelectric line in the precordial leads occasionally established the diagnosis during the early days following the attack when the conventional leads were not distinctive. In these cases there was also associated absence of the Q wave from the apical lead.

Precordial electrocardiograms were of no additional value in the diagnosis of posterior infarction.

For routine work the precordial lead obtained at the apex was found to be of more value than a lead from any other point over the precordium, and with rare exceptions it disclosed as much diagnostic information as multiple precordial leads.

Further investigation is required in the interpretation and application of multiple chest leads in the occasional instances in which the apical lead does not establish the diagnosis.

EFFECT OF BENZEDRINE SULFATE ON GASTRIC EMPTYING AND INTESTINAL ACTIVITY

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In 1937 the Council on Pharmacy and Chemistry of the American Medical Association published a concise review of the literature pertaining to benzedrine.[1] Since the drug is well known, a general discussion of its characteristics is not necessary here.

In a recent paper [2] we reported that in dogs benzedrine given orally decreased the initial emptying time of the stomach to 31 per cent of the normal, but increased the period for final emptying on the average about 14 per cent. Van Liere and Sleeth [3] observed in 3 human subjects the delay in final emptying. More recently Rosenberg, Arens, Marcus and Necheles [4] have confirmed both these observations as to the increased time for final emptying in man and dogs. Investigations conducted on man similar to those previously reported by us led to animal experimentation for an interpretation of these results. We present here our observations concerning the influence of benzedrine on the initial and final gastric emptying in man and evidence from animal experimentation on the manner in which this effect is produced. The action on the stomach, the pylorus and the intact and isolated intestine has been studied.

METHODS

For the work on man 10 medical students were selected and divided into three groups. To avoid the possibility of cumulative effects of the roentgen ray no

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This work was aided by a grant from the Wisconsin Alumni Research Foundation.

1. Present Status of Benzedrine Sulfate, report of the Council on Pharmacy and Chemistry, J. A. M. A. **109**:2164 (Dec. 18) 1937.

2. Beyer, K. H., and Meek, W. J.: Effect of Benzedrine Sulfate on Stomach Activity and Emptying Time, Proc. Soc. Exper. Biol. & Med. **37**:74 (Oct.) 1937.

3. Van Liere, E. J., and Sleeth, C. K.: The Effect of Benzedrine Sulfate on the Emptying Time of the Human Stomach, J. Pharmacol. & Exper. Therap. **62**:111 (Jan.) 1938.

4. Rosenberg, D. H.; Arens, R. A.; Marcus, P., and Necheles, H.: Benzedrine Sulfate: Its Limitations in the Treatment of Spastic Colon and a Pharmacologic Study of Its Effects on the Gastrointestinal Tract, J. A. M. A. **110**:1994 (June 11) 1938.

group was used more often than once in three weeks. The subjects, having omitted breakfast on the morning of the experiment, were given three 10 mg. tablets of benzedrine sulfate each or identical placebos (controls) orally fifteen minutes before the opaque meal.[5]

The meal consisted of 60 Gm. of finely ground Shredded Ralston (wheat) biscuits, 125 Gm. of barium sulfate and 3 Gm. of sugar, thoroughly mixed. Immediately after the administration of the drug, 250 cc. of whole milk was added to the mixture, which was then stirred during the fifteen minute interval before the test. The milk was absorbed by the biscuits, and the meal assumed a thick consistency, which was necessary if we were to obtain initial emptying intervals of significant duration.

The time of initial emptying was determined fluoroscopically as the time from the beginning of deglutition until the first appearance of the meal in the duodenum. The time of final emptying was taken as the interval between the first observation and the time when none of the meal was observed in the stomach.

In the animal experiments 7 trained dogs having Thiry or Thiry-Vella fistulas of the small intestine were used for the studies of the stomach and intestine. Each of 4 dogs had one Thiry or Thiry-Vella fistula. The other 3 had two Thiry fistulas each. In these 3 animals one of the two fistulas had its extrinsic nerve supply intact, while the other was denervated by sectioning the mesentery and stripping the blood vessels to the segment.

Gastric responses were measured by the balloon-water manometer-tambour method. Air conduction was used and an intragastric pressure of from 120 to 130 mm. of water established. The elasticity of the balloon was never a pressure factor.

The activity of the intact intestine was generally recorded by the balloon-mercury manometer method, water conduction being used. Pressures of from 6 to 10 mm. of mercury were used. In a few instances air conduction and the balloon-water manometer-tambour system were employed, the pressure being less than 30 mm. of water. This was done because Gruber [6] and others have reported variable results in their intestinal work when using pressures of more than 30 mm. of water.

When simultaneous studies of gastric and intestinal response were conducted, 20 to 30 mg. of benzedrine sulfate in not over 10 cc. of distilled water was admitted into the stomach through a second catheter during a normal record. This was followed immediately by 5 cc. of distilled water. A normal record is not affected by 15 cc. of water administered slowly in this manner. In more drastic attempts to demonstrate an effect of benzedrine on the intact intestine a dose of from 5 mg. (total) to 5 mg. per kilogram of body weight was given intravenously. Subcutaneous injections and infusions into the fistulas were also tried.

Intestinal segments from 8 pups and 6 rabbits were used. Strips of jejunum and ileum were kept in an open dish of cool Locke's solution. All records were taken from strips less than ten hours old. Segments of from 2 to 3 cm. in length were suspended by the Magnus method in Locke's solution oxygenated at 37 C.

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5. Benzedrine sulfate and placebos were supplied by the Smith, Kline and French Laboratories, Philadelphia.

6. Gruber, C. M.: The Action of Epinephrine, Tyramine and Ephedrine on the Small Intestine of the Unanesthetized Dog, Before and Following the Administration of Cocaine, J. Pharmacol. & Exper. Therap. **57**:347 (Aug.) 1936.

Pyloric activity was recorded by means of a single balloon type pylorograph similar to those described by Wheelon and Thomas.[7] Thirteen fasting dogs were used in these experiments.

Anesthesia was induced by pentobarbital sodium (30 mg. per kilogram, administered intravenously) for the operations on one group of dogs. These were kept in upper third stage anesthesia during the experiment by means of injections of 30 to 60 mg. of pentobarbital sodium every two to three hours as indicated. The other dogs were decerebrated by the method of Sollmann.[8] This operation, including placement of the pylorograph, was carried out during preliminary anesthesia induced by ether, which lasted about thirty minutes.

To place the pylorograph in position, the abdomen was opened and the duodenum partially sectioned just distal to the pancreas. The pylorograph was then carefully passed up through the duodenum and into the pylorus, one flange of the apparatus being placed on either side of the sphincter. The semirigid pylorograph was loosely anchored at the site of insertion into the duodenum. The duodenal opening was in turn sutured into the abdominal incision in a manner permitting drainage to the exterior. The abdomen was then closed except for the duodenal opening. The pylorograph was finally connected through a water manometer to a recording tambour as in the case of the apparatus used for gastric studies.

Records were not taken until three hours or more after the operation, although the pylorus generally manifested rhythmic activity immediately after the pylorograph was connected to the manometer and pressure adjusted in the system. The purpose of this delay was to give the animals time to recover from the immediate effects of the procedure, to allow for adjustment of pyloric tonus and, in the case of decerebrate dogs, to blow off ether.

Intrapyloric pressures of from 3 to 10 cm. of water were used. The position of the pylorograph was checked at the end of an experiment. Both respiration and blood pressure were recorded.

RESULTS

Experiments on Man.—The table represents the data on this portion of the work. The average initial emptying time was decreased from 4.8 to 2 minutes, a decrease of 58.3 per cent. In other words, benzedrine reduced the interval of 41.7 per cent of the observed normal. The standard deviations of the results with different subjects and at different times with a single subject were approximately the same, that for the normal subjects being $\pm$ 1.1 minute and that for a subject after administration of benzedrine $\pm$ 0.4 minute.

The average final emptying time was increased 21 per cent by the drug. The greatest individual increase in final emptying was 39 per cent. In 2 cases there was no signficant difference between the emptying time in the corresponding control experiment and that following administration of the drug. The normal variations for a single subject exhibited

7. Wheelon, H., and Thomas, J. C.: (*a*) Observations on the Motility of the Antrum and the Relation of Rhythmic Activity of the Pyloric Sphincter to That of the Antrum, J. Lab. & Clin. Med. **6**:124 (Dec.) 1920; (*b*) Observations on the Motility of the Duodenum and the Relation of Duodenal Activity to That of the Pars-Pylorica, Am. J. Physiol. **59**:72 (Feb.) 1922.

8. Sollmann, T.: A Method of Bloodless Decerebration, J. Pharmacol. & Exper. Therap. **23**:153 (March) 1924.

a mean value of 16 minutes, with a standard deviation of ± 14 minutes. The mean variation for a single subject after administration of benzedrine was 30 minutes, and the standard deviation was ± 19 minutes. This variation seemed to be independent of body weight for the men. Each of the two young women exhibited an increase in the time for final emptying greater than the combined average for the whole group. While the delay in final emptying after benzedrine is definite, it is not as great as the 57 to 436 per cent reported as due to atropine [9] or the 72.8 to 118 per cent delay following administration of ephedrine.[10]

Animal Experimentation.—Stomach: Benzedrine sulfate given orally in solution had a twofold action on the dog's stomach, as shown in figure 1. The initial response usually occurred within about 8 minutes after the drug was given. This was one of increased rate, increased

Effect of Benzedrine Sulfate (30 Mg., Given Orally) on the Initial and the Final Period of Gastric Emptying in Man

	Initial Emptying				Final Emptying					
	Controls		Effect of Benzedrine		Controls			Effect of Benzedrine		
		Average		Average		Average Time			Average Time	
Subject	No. of Trials	Time, Min.	No. of Trials	Time, Min.	No. of Trials	Hr.	Min.	No. of Trials	Hr.	Min.
L. E. F.	2	5.5	1	2.5	2	4	52	2	5	56
W. B. C.	2	6.5	2	2.0	2	3	34	2	4	04
E. L. K.	2	6.5	1	2.0	2	4	05	1	4	17
S. P. H.	2	3.5	2	2.5	2	3	23	2	4	03
G. G. C.	2	3.0	2	2.0	2	4	23	2	6	06
E. W.*	2	4.5	2	1.5	2	5	11	2	6	32
N. A. F.	2	5.0	2	2.0	2	4	35	2	4	27
E. S.*	2	4.0	2	2.0	2	3	40	2	5	22
J. H. A.	2	5.0	2	2.0	2	3	32	2	4	33
M. J. C.	2	4.0	2	1.5	2	3	45	2	3	47
Total..	20		18		20			19		
Average		4.8		2.0		4	05		4	57

* Female.

tonus and often increased amplitude of contraction. The effect of increased rate and tonus was to elevate the mean intragastric pressure during this period. However, an inhibitory secondary effect followed within forty minutes after administration of the drug, from which the stomach did not generally recover completely for over an hour. During this secondary phase there was marked inhibition, even to cessation of activity, tonus returning to or falling below its state previous to the influence of the drug.

Intestine: We have not been able to demonstrate consistently any influence of the drug on the intestine in situ even in toxic doses (5 mg.

9. Herrin, R. C.: The Effect of Atropine and Pilocarpine on the Emptying Time of the Human Stomach, Am. J. Physiol. **115**:104 (March) 1936.

10. Van Liere, E. J.; Lough, D. H., and Sleeth, E. K.: The Effect of Ephedrine on the Emptying Time of the Human Stomach, J. A. M. A. **106**:535 (Feb. 15) 1936.

per kilogram, administered intravenously). Figure 1 illustrates the refractoriness of a normal Thiry-Vella fistula to the agent.

In figure 2 is seen the response to the drug of the isolated intestine from the dog and rabbit. Benzedrine regularly increased amplitude of

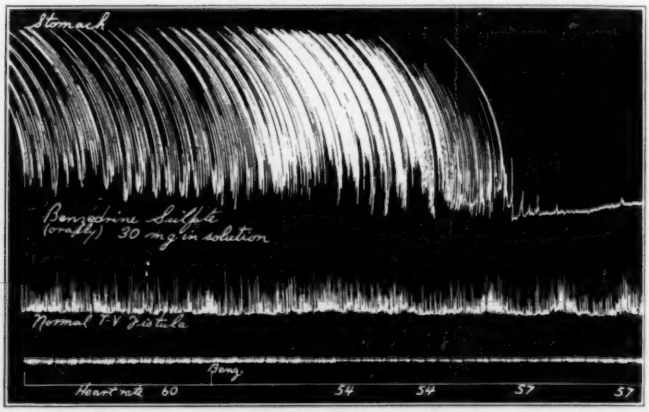

Fig. 1.—Effect of benzedrine sulfate, 30 mg. administered orally, on the activity of the stomach (above) and of a normal Thiry-Vella fistula (below). The heart rate is noted below the base line. The time is indicated in five second and one minute intervals.

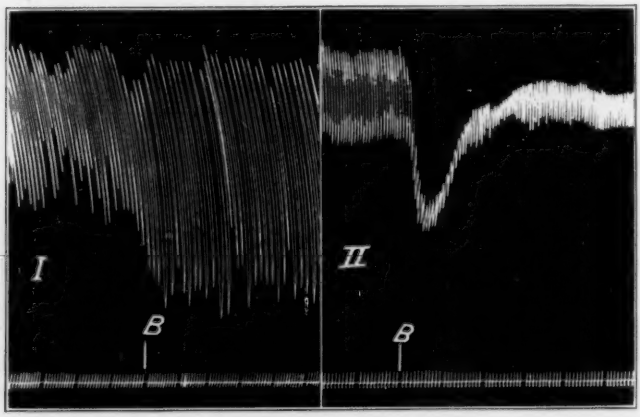

Fig. 2.—Effect of benzedrine sulfate (in a concentration of 1:12,500) on isolated intestinal strips from the dog (*I*) and the rabbit (*II*). Segments were suspended in Locke's solution oxygenated at 37 C. Time is indicated in five second and one minute intervals.

contraction and decreased tonus and rate of rhythmic activity of segments from the dog. It decreased the amplitude and, slightly, the rate of rhythmicity of intestinal strips from the rabbit. Decrease in tonus, in about half of twenty strips, was usually preceded by a marked initial drop. In the other half tonus was either not affected or only slightly increased. Effective concentrations were found to be 1:8,000 to 1:35,000, 1:12,500 usually being used. Detrick and his co-workers [11] found that in dilutions of 1:500,000 to 1:100,000 benzedrine caused inhibition of segments from the duodenum, ileum and colon of cats but that these concentrations had no effect on tissues from the rabbit, rat or guinea pig. Differing somewhat with these results, Boyd [12] reported that concentrations of from 1:10,000 to 1:100,000 predominantly caused a prolonged spastic type of contraction of the virgin guinea pig uterus and of intestinal strips from the rabbit.

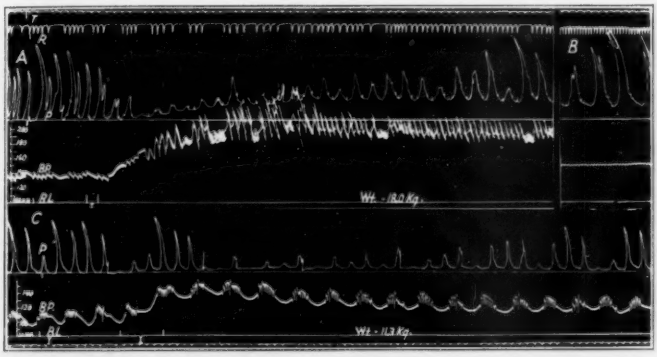

Fig. 3.—Effect of initial intravenous injections of benzedrine sulfate on the pylorus, blood pressure and respiration. *A*, 0.44 mg. per kilogram, rate of injection 3.78 mg. per kilogram per minute; *C*, 0.178 mg. per kilogram, rate of injection 0.378 mg. per kilogram per minute. *A* and *B* are from a dog under anesthesia induced by pentobarbital sodium, *B* being taken thirty minutes after the injection shown by *A*. *C* is from a decerebrate dog. *R* represents respiration; *T*, time in one minute and five second intervals; *P*, pyloric activity; *B.P.*, blood pressure in mm. of mercury; *B.L.*, base line for the blood pressure, and *I*, the duration of the injection.

Pylorus: Since the results for the dogs under anesthesia induced by pentobarbital sodium and those for the decerebrated animals were

11. Detrick, L. E.; Millikan, R.; Modern, F. S., and Thienes, C. H.: On the Pharmacology of Phenylisopropylamine (Benzedrine), J. Pharmacol. & Exper. Therap. **60**:56 (May) 1937.

12. Boyd, E. M.: The Effect of Benzedrine Sulphate on the Bowel and Uterus, Am. J. M. Sc. **195**:445 (April) 1938.

qualitatively the same, they may be considered together. Benzedrine increased the tonus and inhibited the amplitude of contraction of the rhythmic pylorus (fig. 3). Amplitude of contraction was affected by smaller doses of the drug than was tonus. The duration of action was dependent on the concentration of the drug; however, a normal or even increased amplitude preceded the return of normal tonus. In animals anesthetized with pentobarbital sodium the pylorus was not usually affected unless the concentration of the agent was sufficient to cause on the average a 49 per cent rise in blood pressure (approximately 0.23 mg. per kilogram at an initial intravenous injection of 15 seconds' duration). However, pressor increases of 31 per cent were sometimes accompanied by a slight decrease in amplitude. We do not mean to imply that blood pressure was a factor in causing the pyloric response, but to point out on a pressor basis the relative insensitiveness of the pylorus to the drug.

Blood Pressure and Respiration: A complete analysis of data on blood pressure and respiration does not belong in this paper. Briefly, at the height of the pressor effect vagal beats generally occurred, especially after initial injections, and in 1 instance ventricular rhythm was prolonged. The respiratory rate was always increased by benzedrine under these conditions.

COMMENT

Normal gastric emptying is now generally believed to be dependent on the relation between intragastric pressure and resistance at the pyloric sphincter and possibly the duodenal bulb. Many factors are known to modify this pressure-resistance relation. The tandem balloon studies of Wheelon and Thomas [7] and Meschan and Quigley,[13] analyzing the part played by these various factors, have been of particular interest.

In terms of this relation, rate of evacuation may be increased by: (1) increased intragastric pressure, (2) decreased resistance at the pylorus and upper part of the duodenum, (3) a combination of these two conditions or (4) disproportion increase or decrease of intragastric pressure and pyloric resistance so that the gastric influence remains dominant. Decrease in the rate of emptying may be explained similarly by reversing the conditions. Thus the rate of emptying is dependent on the combined influences of the factors involved. The increase in initial rate due to benzedrine may be explained by the fourth condition just listed, the increased pyloric resistance not being sufficient to overcome the increased intragastric pressure due to the drug. The delay in final emptying is obviously due to the gastric inhibition.

13. Meschan, I., and Quigley, J. P.: Spontaneous Motility of the Pyloric Sphincter and Adjacent Regions of the Gut in the Unanesthetized Dog, Am. J. Physiol. **121**:350 (Feb.) 1938.

Myerson and Ritvo,[14] from fluoroscopic and roentgenographic evidence, suggested that the stomach empties more rapidly under the influence of benzedrine because peristaltic activity of the stomach is only slightly decreased and the sphincter is relaxed. From these observations, they recommended benzedrine for the relief of pylorospasms, facilitating roentgenoscopy of adjacent regions. Since gastric emptying is the result of several factors of resistance and pressure, it is doubtful if tonicity of the pylorus or stomach can be accurately deduced from fluoroscopic determinations.

We have found that gastric activity and intragastric pressure are increased at first after ingestion of benzedrine. Our experiments indicate that benzedrine would, if anything, tend to increase tonicity and inhibition of pyloric rhythmicity rather than relieve it. However, the marked increase in initial rate of evacuation reported by us here and previously suggests that the increased tonicity of the pylorus is not sufficient to overcome the effect of the initial gastric stimulation by the drug.

SUMMARY

In man benzedrine sulfate was found to decrease the time for initial emptying of the stomach to about 42 per cent of the observed normal and to increase the average time for final emptying 21 per cent.

The decrease in initial emptying time of the normal stomach following administration of benzedrine is probably due to the primary increase in tonus and activity of the stomach raising intragastric pressure and forcing the contents through a pylorus the tonus of which, if altered by the drug, may relatively be only slightly increased, rhythmicity being correspondingly diminished. The delay in final emptying is due to secondary inhibition of the stomach and possibly increased pyloric tonus. While the stomach does not fully recover from the secondary inhibition for over an hour, final emptying is not prolonged to a very significant extent.

Only by using excised intestinal strips and concentrations unapproachable in the normal animal could we demonstrate any effect of the drug on the intestine.

These results suggest that what value benzedrine has in overcoming functional pylorospasm of a moderate degree is probably due to initial gastric stimulation overcoming pyloric resistance rather than to any direct inhibiting effect on pyloric tonus.

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14. Myerson, A., and Ritvo, M.: Benzedrine Sulfate and Its Value in Spasm of the Gastro-Intestinal Tract, J. A. M. A. **109**:23 (July 4) 1936. Ritvo, M.: Drugs as an Aid in Roentgen Examination of the Gastro-Intestinal Tract: The Use of Mecholyl, Physostigmine, and Benzedrine in Overcoming Atonicity, Sluggishness of Peristalsis, and Spasm, Am. J. Roentgenol. **36**:868 (Dec.) 1936.

NEPHROSIS DUE TO CARBON TETRACHLORIDE

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The number of clinical reports of cases of carbon tetrachloride poisoning with renal symptoms comparable to those of acute nephritis or toxic nephrosis is steadily increasing. Although symptoms referable to hepatic damage are usually present in such cases, they are soon overshadowed by signs indicating severe renal damage. The intoxication is due either to inhalation in a poorly ventilated room of fumes of carbon tetrachloride used for cleaning purposes or in fire extinguishers or to ingestion of this chemical.

The clinical symptoms and laboratory findings observed in such cases are so characteristic and uniform that the correct diagnosis can be made without an adequate clinical history of carbon tetrachloride poisoning. Indeed, the clinical picture sometimes prompts specific inquiries pertaining to the use of this chemical. The patients suffer from headache, dizziness, general malaise, fever and sometimes irritation of the nasal and conjunctival mucous membranes. Soon there appear signs of gastric irritation characterized by nausea, vomiting, diarrhea and not infrequently hematemesis; jaundice sets in and may attain a considerable degree of severity. After several days, during which the gastrointestinal symptoms remain more or less stationary and the jaundice increases, there appear clinical signs of renal involvement, such as oliguria, progressing sometimes to anuria, epileptiform convulsions, hypertension and generalized edema; cyanosis and pulmonary edema may develop, and uremic coma is not rare. Commonly a hemorrhagic diathesis is observed. Not all these symptoms may be present, but most of them are observed in the majority of cases.

LABORATORY FINDINGS

The nonprotein nitrogen content of the blood is elevated, with reported values up to over 200 mg. per hundred cubic centimeters; the urea content, up to about 200 mg.; the uric acid content, up to 12 mg.; the creatinine content up to 10 mg., and the inorganic phosphorus content up to 11 mg. The values for sugar vary from 125 to 155 mg. per hundred cubic centimeters. The chloride value is around 500 mg., the calcium value between 9 and 10 mg. and the cholesterol value about 140

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mg. Sometimes the reported values for phospholipids are low, and the ratio of ester cholesterol to total cholesterol is diminished. Some authors report a lower levulose tolerance and a reduced fibrinogen content. The guanidine level is elevated. The value for protein is within normal limits; the carbon dioxide–combining power is lowered, varying between 25 and 42 volumes per cent. The icteric index varies between 12 and 30 in different cases. In the early stage there may be polycythemia, which is sometimes followed by anemia, depending on the degree of hepatic damage. There is leukocytosis, the count ranging from about 10,000 to 35,000 per cubic millimeter, with polymorphonuclears predominant.

The blood pressure is markedly increased, and values from 200 to 300 mm. of mercury, with a high diastolic pressure, are not unusual.

The urine is scanty and contains albumin; often there are red blood cells, white blood cells and casts.

Most of the patients reported on in the literature recovered even after having been in uremic coma. Recovery is rapid and complete; but leukocytosis may persist and the renal function may be below normal for some time. The improvement is accompanied by the return to normal values for nitrogenous waste products in the blood and by the return of the icteric index to normal; the urine increases in amount and becomes free from albumin, red blood cells, white blood cells, bile and casts.

REPORT OF CASES

Within the last year 3 patients with carbon tetrachloride poisoning have been observed in the Presbyterian Hospital. Two of the patients died, and autopsies were performed; 1 patient recovered. Dr. W. W. Palmer has given me permission to publish the following case histories from the records of the hospital:

CASE 1.—A 71 year old white man, a photographer, was admitted to the hospital on March 21, 1937, because of painless jaundice following intake of some fluid containing carbon tetrachloride eight days previously (the exact amount of carbon tetrachloride ingested could not be ascertained).

Past History.—He had always been in good health and active. There was, however, a history of chronic alcoholism.

Present Illness.—There were no immediate effects after the chemical was swallowed; nausea and vomiting began the following night and continued for eight days, until admission to the hospital. Jaundice appeared on the second day and anuria on the sixth day. There had been no bowel movement during the past eight days. There had been complete anorexia during this period. The patient was semistuporous on entry.

Physical Examination.—The temperature was 97.4 F., the pulse rate 80 and the respiratory rate 22. The blood pressure was 140 systolic and 85 diastolic. The patient complained of constant nausea and was intensely jaundiced. The head and chest were essentially normal except for pulmonary emphysema. The abdomen

was distended, with the skin drawn tight; there were shifting dulness and a definite fluid wave. The bladder was distended. The edge of the liver was at the costal margin. No tenderness or mass was noted.

Laboratory Findings.—Examination of the blood showed: hemoglobin, 120 per cent; red blood cells, 5,600,000 (the cells were normal as to size and shape but showed some variation in the hemoglobin content); white blood cells, 13,680; polymorphonuclears, 91 per cent; lymphocytes, 7 per cent, and mononuclears, 2 per cent. There was a normal number of platelets. Chemical analysis of the serum showed: inorganic phosphorus, 6.5 to 7.8 mg. per hundred cubic centimeters; bilirubin, 13.6 to 14 mg.; chlorides (as sodium chloride) 500 mg.; calcium, 8.7 mg.; sugar, 126 mg.; nonprotein nitrogen, 165 mg.; phosphatase, 6.3 Bodansky units; carbon dioxide, 44 volumes per cent; total protein, 7.2 Gm.; albumin, 3.7 Gm.; globulin, 3.5 Gm., and euglobulin, 1.1 Gm. Urinalysis showed specific gravity of 1.015. There were a 3 plus reaction for albumin, a 0 to 1 plus reaction for acetone and a 2 plus reaction for bile. There was no sugar. There were a few red blood cells, white blood cells and cellular casts. The urine was straw colored. The stools were soft and light yellow. There were no gross blood, mucus, parasites or ova. There was a 1 plus reaction for bile. The guaiac test gave a negative reaction.

Course.—The patient was given fluid containing dextrose parenterally, but in spite of large infusions the urinary output remained small. On the tenth day of illness he was found gasping for breath. He was cyanotic and had prolonged expirations. The lungs were clear; the pulse rate was slow and regular. He became progressively more cyanotic and stopped breathing ten days after taking the carbon tetrachloride. The final clinical diagnosis was carbon tetrachloride poisoning, acute yellow atrophy of the liver with cholemia, nephrosis and pulmonary emphysema.

Autopsy Data.—Examination was performed three hours after death.

Gross Examination: The skin was intensely and uniformly icteric. The thorax was barrel shaped. There were no other relevant external findings.

The peritoneal cavity contained 2,000 cc. of clear yellow fluid. The peritoneal surfaces were smooth and glistening, the organs were normally disposed and the edge of the liver was at the costal margin. The pleural cavities and pericardial sac were normal. The heart, spleen, pancreas and adrenal glands were normal. The aorta was arteriosclerotic, and the lungs were emphysematous. The liver weighed 1,220 Gm.; it was definitely smaller than normal and soft. The surface was finely granular, the parenchyma was intensely jaundiced and the central zones were sunken and dark reddish brown. There was a slight increase in the amount of fibrous tissue about the portal canals. Numerous tiny yellowish flecks were seen in the midportion of the lobules. No gross changes were apparent in the biliary passages or vessels. The gallbladder was normal. The kidneys weighed 160 Gm. (right) and 200 Gm. (left), respectively. When the capsule was incised, the renal tissue bulged through, suggesting swelling of the parenchyma. The kidneys were of similar appearance. The capsules stripped easily, leaving a surface which was in places slightly irregular. The parenchyma was a dull reddish brown, through which a greenish tint was observed. On section the kidneys appeared swollen. The cortex was wide, pale and firm, and its striations were blurred, while those of the pyramids were distinct. The centers of several of the pyramids showed yellow streaks parallel to the striations. There were numerous indistinct yellowish areas throughout the cortex. The blood vessels were not unusual. A double pelvis was found on the right side, with the ureters

uniting to form a common ureter 3 cm. below the calices. The mucosa of the pelves and ureters was normal. The bladder was small and contracted and the mucosa greenish yellow. There were ecchymoses in the posterior wall. The prostate was enlarged; otherwise it was not remarkable. The testes, epididymides and seminal vesicles were normal. The esophagus was normal. The mucosa of the stomach was covered with a thick layer of mucus; the mucosa underneath appeared normal. The small and large intestines were grossly normal. The brain and spinal cord were not removed.

Chemical analyses of the hepatic and renal tissue for mercury, arsenic and lead showed no excessive amounts.

Microscopic Examination: The liver showed extensive central necrosis, degeneration of the cells and early regeneration in the periphery of the lobule. There

Fig. 1.—Cross section of the kidney, showing distention of the glomerular spaces with albuminous material, and casts and granular precipitate in the lumens of the tubules; × 60.

were hemorrhages in the central areas. No evidence of proliferation of the bile ducts was seen. Bile plugs were present in some of the canaliculi. In the kidneys the glomeruli were somewhat larger than normal, and the capillary loops were congested. The tufts were rather poor as to cells. The space of Bowman was greatly distended with pink-staining granular precipitate, which sometimes was compressing the tufts. The epithelial cells lining the spaces were sometimes swollen, projecting into the lumens. The basement membrane of the glomeruli appeared swollen and irregularly thickened (fig. 1). The epithelial cells of the proximal convoluted tubules were swollen, granular or vacuolar, and the lumens contained granular precipitate or hyaline casts, which sometimes were bile stained. The lumens of Henle's loops and those of the distal convoluted

tubules were greatly distended with hyaline and cellular casts, which sometimes were bile stained. The lining cells of these tubules were irregular as to size and were frequently sloughed off as single cells or in toto; not infrequently a new lining had been formed, so that the casts were surrounded by a double layer of epithelial cells, most of which showed signs of degeneration. A rare mitotic figure could be seen in the lining cells. Many of the collecting tubules contained hyaline or cellular casts. In addition to the casts, bodies of various sizes were free within the lumens of the convoluted tubules and those of Henle's loops; they were either pale yellowish green or more or less deeply stained with hematoxylin. These concretions showed a definite radial arrangement and were brilliantly doubly refractive. There were edema of the cortex and moderate congestion of the pyramids. Stains showed a small number of fine fat droplets in the lining cells of Henle's tubules. With von Kossa's stain the concretions became black. The other organs showed no relevant pathologic changes.

Anatomic Diagnosis.—The diagnosis was poisoning due to carbon tetrachloride; central necrosis of the liver; jaundice; ascites; nephrosis due to carbon tetrachloride; advanced arteriosclerosis of the aorta, with calcification and ulceration; chronic bronchitis; mild bronchiectasis; pulmonary emphysema; mild hemorrhagic cystitis, and congenital malformation of the right kidney (double pelvis).

CASE 2.—A 37 year old Negress, a housemaid, was admitted on May 22, 1937, because of vomiting, diarrhea, chills, fever and painful muscle spasms for forty-eight hours.

Family History.—The family history was irrelevant.

Past History.—Spontaneous abortion, necessitating a pelvic operation, occurred in 1918. There was a history of chronic alcoholism, frequent excesses being customary.

Present Illness.—Three days before entry she was cleaning dresses with carbon tetrachloride in a close, stuffy room for three hours. Afterward she drank a glass of cold milk and suddenly had an attack of moderately severe cramplike pain, with a sense of fulness in the epigastrium. Soon she began to vomit and had vomited repeatedly since. Although she was usually constipated, diarrhea developed, with seven to eight movements a day for the past forty-eight hours. On the second day of her illness she began to have severe pain, with spasms of the muscles, and was seen by a physician. She had a carpopedal spasm, and the Chvostek sign was elicited. Calcium lactate and phenobarbital failed to relieve the pain.

Physical Examination.—The temperature was 103.6 F., the pulse rate 88, the respiratory rate 26 and the blood pressure 100 systolic and 56 diastolic. The patient was poorly developed and thin; she was excited and terrified and was crying. She was breathing rapidly while lying in bed with her arms flexed across her chest and her hands showing carpopedal spasm. The pupils were contracted, irregular and fixed. The conjunctiva was injected, and there was milky opacity of the right lens. No jaundice was evident. The breath smelled of acetone. The teeth were carious. The neck was not stiff, and the thyroid gland was not enlarged. The lungs were clear. The heart was normal, with a rapid rate. The abdomen was tense; there was slight tenderness in the right lower quadrant on depression, without rebound tenderness or spasm. The reflexes were normal. The Chvostek and Trousseau signs were elicited.

Laboratory Findings.—The laboratory findings are given in table 1. A specimen of the cleaning fluid was examined and was found to be carbon tetrachloride.

Course.—There was an almost complete shutdown of the function of the kidneys for a period lasting for several days, in spite of the administration of large infusions of Ringer's solution and of 10 per cent solution of dextrose. It was thought that the patient was suffering from the effects of carbon tetrachloride poisoning due to inhalation of vapors while working in a poorly ventilated room. Both the liver and the kidneys were thought to be affected, because there were bile in the serum and urine, almost complete anuria, albumin and blood elements in the urine and marked nitrogen retention. The generalized tetany was thought to be related to cholemia. Forcing of fluids was continued, and after three

TABLE 1.—*Laboratory Findings (Case 2)*

	5/22	5/24	5/29	6/2	6/8	6/28
Carbon dioxide content, vol. %	54.5	43.3	....	....	....	....
Chlorides (as sodium chloride), mg. per 100 cc.	478	515	602	....	575	....
Inorganic phosphorus, mg. per 100 cc.	5.6	4.2	4.3	3.9	2.4	....
Sodium, mEq. per L.	124.5	120.0	....	....	....	....
Potassium, mEq. per L.	....	6.1	....	....	....	....
Calcium, mg. per 100 cc.	9.7	8.1	....	8.8	9.8	....
Total lipids, mg. per 100 cc.	....	1,185	....	684	....	....
Phospholipids, mg. per 100 cc.	....	236	....	190	....	....
Neutral fat, mg. per 100 cc.	....	760	....	270	....	....
Total fat, mg. per 100 cc.	....	115	....	204	....	....
Free cholesterol, mg. per 100 cc.	....	77	....	87	....	....
Combined cholesterol, mg. per 100 cc.	....	138	....	117	....	....
Bilirubin (direct), mg. per 100 cc.	4.5	4.7	3.5	4.0	2.0	Trace
Phosphatase, Bodansky units per 100 cc.	4.7	4.0	4.4	5.0	4.6	....
Nonprotein nitrogen, mg. per 100 cc.	63	82	94	66	37	26
Protein, Gm. per 100 cc.	7.8	5.9	....	....	....	7.5
Albumin, Gm. per 100 cc.	4.4	3.3	....	....	....	3.9
Globulin, Gm. per 100 cc.	3.4	2.6	....	....	....	3.6
Euglobulin, Gm. per 100 cc.	0.7	0.5	....	....	....	....
Sedimentation rate, mm.	10	....	....	....	60	62
Hemoglobin, %	85	65	57	....	70	67
Red blood cells, million per cu. mm.	4.3	3.6	3.3	....	3.9	3.4
White blood cells, per cu. mm.	13,250	6,900	22,700	13,250	6,700	6,900
Polymorphonuclears, %	87	51	82	58	60	51
Lymphocytes, %	5	42	13	33	29	42
Monocytes, %	4	5	3	6	10	5
Eosinophils, %	2	2	1	2	0	0
Basophils, %	2	0	1	1	1	2
Platelets	Normal	Normal	Normal	Normal	Normal	Normal
Blood pressure	100/50	130/78	112/80	....	100/70	94/64
Urine: albumin	++++	+++	+	0	+	0
bile	+	0	0	....	....	....
red blood cells	+	+	+	0	0	....
white blood cells	+	+	+	+	+	0

days of anuria the patient began to pass urine; after the first week the output of urine rose to over 1,000 cc. a day. The nonprotein nitrogen reached values close to 100 mg. per hundred cubic centimeters at the end of the first ten days, but with continued treatment it began to drop; at the same time the values for blood urea and nitrogen, inorganic phosphorus and bilirubin returned to normal. Eleven days after the onset, fever developed, and she showed signs of consolidation of the lungs, without dyspnea or cough. An electrocardiogram taken at this time suggested myocardial damage. The patient was kept in bed as long as the electrocardiographic changes were present; she had a low grade fever and an elevated sedimentation rate, for which residual hepatic damage was held responsible. She was allowed to go home on June 30 for further rest, forty-six days after the beginning of her illness. She was seen in the clinic on July 19

and seemed much improved. Her only complaints were of slight swelling of the ankles and a capricious appetite.

The final clinical diagnosis was poisoning due to carbon tetrachloride, toxic hepatitis, acute renal tubular damage, toxic myocarditis, lobular pneumonia (organism unknown) and cirrhosis (?) of the liver.

CASE 3.—A 35 year old Negro, a dry cleaner and interior decorator, was admitted to the hospital on Oct. 10, 1937, because of dyspnea and cough, with bloody sputum, of eight days' duration. Most of the following history was supplied after the patient's death by his co-worker and by his physician.

The patient was well until eight days before entry, when he returned from work and noted dyspnea. He had been cleaning furniture and draperies with a cleaning solution containing perchlorethylene and trichlorethylene or carbon tetrachloride. According to the statement of his physician, he had run out of the cleaning fluids which he ordinarily used and had purchased several gallons of carbon tetrachloride in order to finish his work. Several hours after this exposure to the vapors of the chemical, which had lasted for several hours, he became acutely ill, with headache, dizziness and malaise; he was nauseated and vomited repeatedly. His pulse rate at that time was over 100 and his blood pressure about 160 systolic. The physician prescribed sedatives and digitalis, which gave no relief. The next day the patient was still nauseated and was vomiting. Several days after this his physician saw him again and noticed a peculiar dusky discoloration of the skin; the patient still complained of gastrointestinal symptoms. Both his co-worker and his physician stated that he was a steady and heavy drinker. Eight days after the onset of his illness he was sent to the hospital by another physician, with a diagnosis of probable bleeding gastric ulcer or early pulmonary tuberculosis. Just previous to entry he had had some difficulty in voiding, the nature of which was not ascertained.

Physical Examination.—The temperature was 99.4 F., the pulse rate 130, the respiratory rate 36 and the blood pressure, 220 systolic and 125 diastolic. The patient appeared well developed and well nourished. He was thrashing about in bed, gasping for breath. He coughed frequently, raising bloody, frothy sputum. The skin was moist and warm. The pupils were small (morhpine). There were large, symmetric scleral hemorrhages lateral to the corneas. The pharynx was edematous and injected. No local or general glandular enlargement was noted. The trachea was in the midline, and the thyroid gland was normal. The heart was enlarged to the right and to the left. There was marked gallop rhythm, the rate was rapid and a systolic apical murmur was heard. The lungs were normal to percussion; wet râles were present throughout both lungs, front and back. The breath sounds were normal. The liver was enlarged, extending to the umbilicus. There were no other masses. No edema was present in the extremities. The radial pulses were equal; the nail beds were cyanotic. There were symmetric macular ecchymoses on the lateral aspect of the upper portion of both arms.

Laboratory Findings.—The blood count showed: hemoglobin, 97 per cent; red blood cells, 5,750,000 (cells and platelets, normal); white blood cells, 36,000; polymorphonuclears, 95 per cent, and lymphocytes, 5 per cent. The nonprotein nitrogen content was 188 mg. per hundred cubic centimeters. The sedimentation rate was 18 mm. The Wassermann test gave a negative reaction.

Course.—Because of the scleral and dermal ecchymoses, purpura was suspected. Pericardial hemorrhage with tamponade was considered a possibility. However, no definite clinical diagnosis could be made. Phlebotomy (360 cc.) was per-

formed, and he was given 8 cc. of digalen intramuscularly; he responded to that and became quieter with additional doses of morphine. His lungs appeared to clear somewhat, and he rested quietly. Soon, however, pulmonary edema developed, and he died fifteen hours after entry. The clinical impression was as follows: hypertensive cardiovascular disease with cardiac failure (?) and acute nephritis (?) of unknown type.

Autopsy Data.—The examination was performed eight hours post mortem.

Gross Examination: Externally no abnormalities were noted except for the ecchymoses and the slight icterus of the scleras. The body cavities contained no fluid, and the visceral surfaces of the organs were smooth and glistening. There were petechial hemorrhages in all the serous membranes. The heart was normal. The aorta showed early atheromatous changes. The lungs weighed 1,000 Gm. each and showed marked edema and early consolidation. The spleen, pancreas and adrenal glands were normal. The liver weighed 1,900 Gm. It was soft, and on cut section the central portion of the lobules was dark red and sunken, while

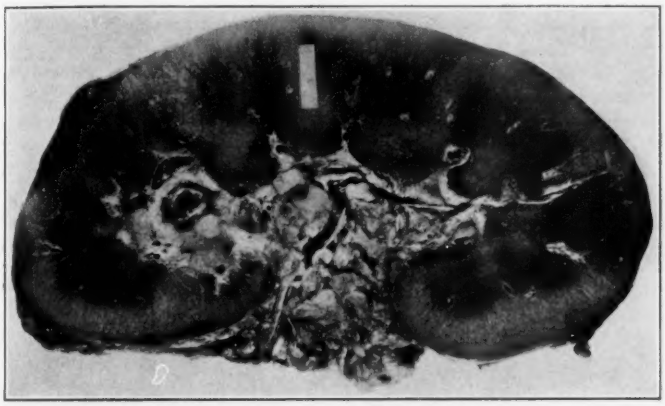

Fig. 2.—Gross appearance of the kidney on cross section.

the periphery showed an ocher yellow tint. The bile ducts and blood vessels were not remarkable. The gallbladder and common duct were normal. The kidneys weighed 220 Gm. each, and their capusles stripped easily (fig. 2). There was a large extracapsular hemorrhage in the region of the lower pole of the left kidney, and petechiae and ecchymoses were present on the surfaces of both kidneys. The organs were swollen, and on cut section the cortex was bulging. The consistence was much softer than normal. The cortex measured 1 to 1.3 cm. in width, and its radial structure was obscured; it was a pale yellowish brown. The pyramids were pink, and their striations appeared less distinct than normal. The renal pelves were of normal size and showed many ecchymoses and petechiae. The ureters were normal. The bladder was distended with 500 cc. of cloudy urine containing flecks of fibrin; its mucosa was swollen and showed many ecchymoses. The urine contained red blood cells, white blood cells and casts. There were a 3 plus reaction for albumin and a 2 plus reaction for bile. The prostate, testes and seminal vesicles were normal. The mucosa of the stomach was dark red; its folds were prominent and were covered with a layer of mucus. The mucosa

of the small intestine and the appendix appeared normal. The mucosa of the cecum was edematous and showed some ecchymoses. There was a large diffuse hemorrhage into the tissues of the root of the mesentery. The cervical organs were normal. The marrow of the femur was fatty and that of the vertebra grayish red. The brain and spinal cord were not removed. Postmortem culture of blood was sterile. Hepatic and renal tissues were analyzed for arsenic and mercury, and normal values were reported.

Microscopic Examination: The heart and aorta were normal. The lungs showed early lobular pneumonia, sometimes with the formation of a hyaline membrane. Edema fluid was present in most alveoli of both lungs, and there was slight acute bronchitis. The liver showed marked central necrosis, with secondary distention of the central sinusoids. There were degenerative changes in the hepatic cells in the intermediate zone, without signs of regeneration. Fatty changes were noted in the hepatic cells about the portal canals. Within the central necroses there were many phagocytic cells holding golden yellow pigment granules, which gave a partially positive reaction for iron; there was condensation of reticular fibers in the central areas. The gallbladder and pancreas were normal. The adrenal glands and the spleen were normal. In the kidneys the capillaries of the glomerular tuft were congested, and the capsular spaces contained much granular precipitate, which was sometimes so abundant as to push aside the tuft. The basement membrane of the glomeruli was swollen and prominent. The epithelial cells lining the space of Bowman were swollen and were projecting into the lumen (fig. 3*A*). The epithelial cells of the proximal convoluted tubules were swollen, granular and vacuolated; rarely, hyaline droplets were seen (fig. 3*B*). Many of the distal convoluted tubules showed necrosis of their lining cells, many of which had sloughed off; there was early regeneration, and rare mitotic figures were present in the lining cells (fig. 4). Most of the convoluted tubules and those of Henle's loops were distended by granular, sometimes hyaline, eosinophilic material. Many small, round concretions showing a radial arrangement were seen in the lumens of these tubules; some of them took the hematoxylin stain, while others did not and were a pale yellowish green (fig. 5*A*). All bodies showed double refraction under the polarizing microscope (5*B*). The stroma of the cortex and medulla was edematous, and the capillaries of the medulla were congested; a few small hemorrhages were present. Many of the tubules of the medulla—especially the collecting tubules—were plugged with granular, hyaline or cellular casts. Extensive hemorrhages were present about the renal pelves, sometimes accompanied by polymorphonuclear leukocytes. Stains for fat showed only a few small droplets in the epithelial cells of the convoluted tubules. Von Kossa stains brought out the concretions in the tubules. The bladder showed hemorrhagic cystitis. The prostate, testes and seminal vesicles were normal. The mucosa of the stomach was congested and showed a few polymorphonuclear infiltrations. The small intestine was normal. There were moderate congestion and edema of the submucosa of the cecum. The thyroid and parathyroid glands were normal. The bone marrow was normal.

Anatomic Diagnosis.—The diagnosis was poisoning due to carbon tetrachloride, central necrosis of the liver; fatty liver; nephrosis due to carbon tetrachloride; edema of the lungs; early acute bronchitis; bilateral lobular pneumonia, and hemorrhages in the lungs, pleura, pericardium, mesentery, renal pelves, retroperitoneum, conjunctiva and skin.

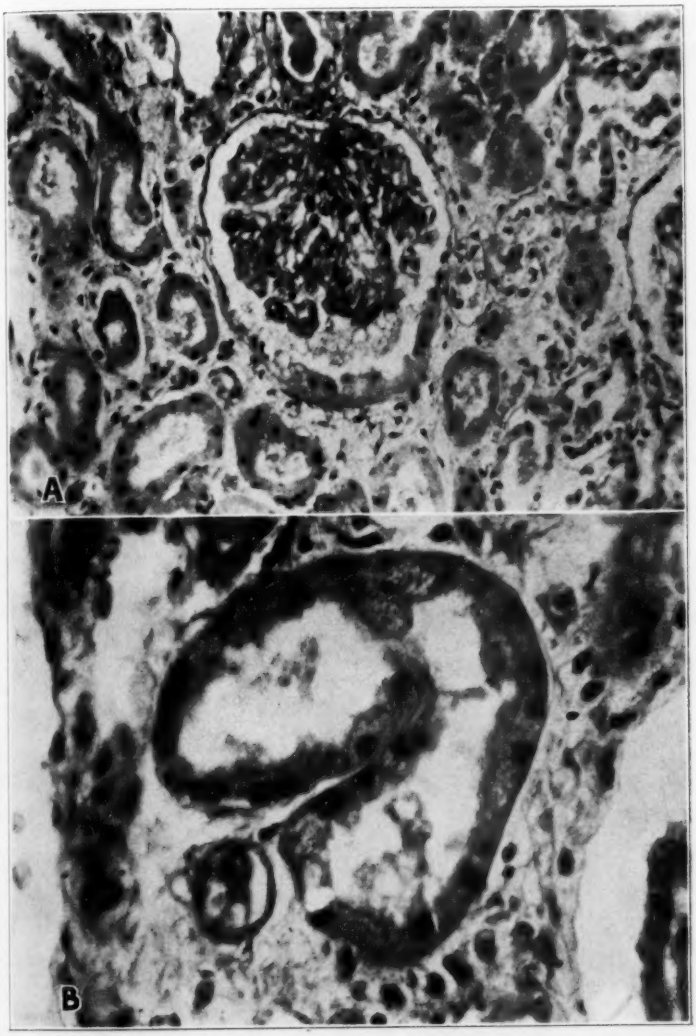

Fig. 3.—*A*, showing albuminous material in the capsular space and swelling of the epithelial cells lining the space of Bowman; × 230. *B*, showing swelling and vacuolation of the epithelial cells of proximal convoluted tubules and edema of the cortical stroma; × 460.

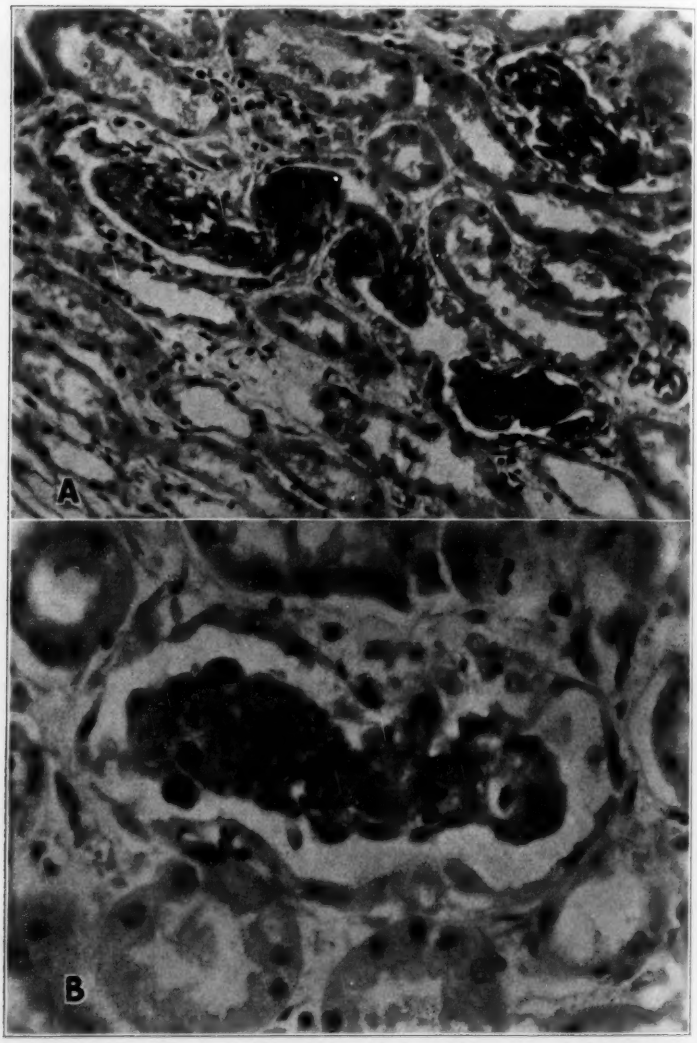

Fig. 4.—*A*, showing granular and cellular casts in the lumens of distal convoluted tubules; × 230. *B*, showing granular and cellular cast in the lumen of a distal convoluted tubule, with partial sloughing of the lining cells; × 460.

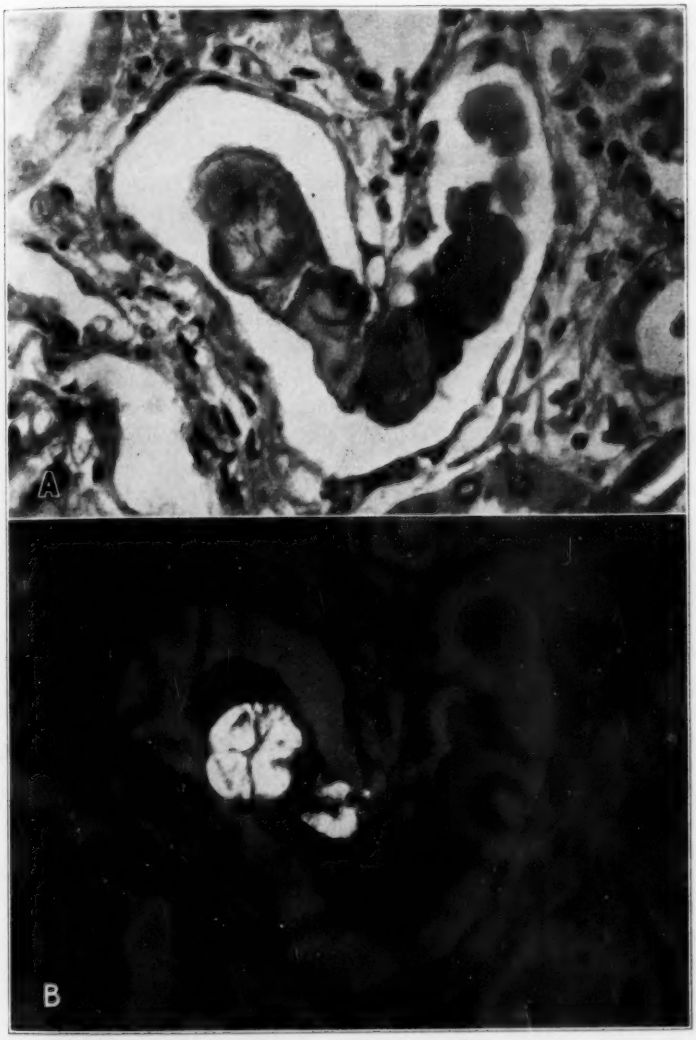

Fig. 5.—*A*, showing a cast and concretions in the lumen of a distal convoluted tubule. *B*, showing double refraction of the concretions under the polarizing microscope; × 460.

COMMENT

In all 3 cases there was remarkable uniformity of the clinical pictures, conforming with the reports of similar cases in the literature. Likewise the pathologic changes in the 2 fatal cases were essentially alike and corresponded with those described by some observers, particularly by McMahon and Weiss.[7] Aside from the lesions in other organs—especially in the liver—there was clinical evidence of functional damage of the kidneys, recognized by the presence of albumin in the urine, oliguria, nitrogen retention, edema and acute hypertension. The albuminous casts within the glomerular spaces and tubules may be considered as anatomic evidence of functional damage of the glomeruli; anatomic changes in the glomerular tufts were not seen. The necrosis of tubular cells was probably due to a greater concentration of the damaging agent after reabsorption of water within the tubular system and was similar to but not so extensive as that seen in mercury bichloride poisoning. Calcification of the necrotic tubular cells—commonly observed in cases of mercury bichloride poisoning and lasting for ten days or longer—is not a feature in nephrosis due to carbon tetrachloride poisoning, perhaps because of its shorter course in fatal cases. Whether the oliguria was due to mechanical obstruction of the tubules by cellular and albuminous casts or to functional disorder is difficult to say. The nitrogen retention and acute hypertension were similar to those observed in case of mercury bichloride poisoning and were probably of similar origin.

The chemical nature of the globular concretions seen in the tubules of the kidneys in the 2 fatal cases has not been identified, and their significance is not clear. Their refractility under the polarizing microscope disappeared quickly after the addition of a few drops of normal solution of hydrochloric acid and vanished slowly after the addition of normal solution of sodium hydroxide. No change could be observed after the addition of 10 per cent acetic acid or any of the organic solvents, such as alcohol, acetone, benzene or xylene. All the bodies were blackened by the von Kossa stain, indicating that they contained either phosphate or calcium or both. After microincineration the organic framework of the concretions was lost, and only specks of a slightly refractive matter were left; after the addition of normal solution of hydrochloric acid, their refraction disappeared. It must be pointed out that similar bodies were occasionally seen in sections of kidneys which showed no pathologic lesions; a few were also observed in a case of mercury bichloride poisoning. It is perhaps the large number of such concretions that is of some significance, and their presence should be checked in the future in cases of carbon tetrachloride poisoning.

Concerning the modes of carbon tetrachloride poisoning, two major ones can be distinguished; intake by mouth and inhalation of fumes.

Absorption through the skin (shampoo, dipping of arms or other methods) should perhaps be considered, but this type is probably always complicated by inhalation of the vapors. An analysis of the cases of carbon tetrachloride poisoning reported in the literature indicates a greater percentage of renal symptoms in cases of poisoning due to inhalation; likewise, the anatomic lesions in the kidneys seem more common in the fatal cases of this type. Data are given in table 2 with regard to all the cases reported in the literature and the 3 present cases. According to Lamson and his associates,[38] the concentration of carbon tetrachloride is greater in the portal circulation than in the general circulation after ingestion of the chemical; in cases of poisoning due to inhalation, the concentrations of carbon tetrachloride reaching the liver and the kidneys are about equal. This may perhaps explain the greater susceptibility of the kidneys in cases of carbon tetrachloride poisoning by inhalation.

While the influence of alcoholism cannot be correctly evaluated, because many of the reports omit reference to this point, it seems definite

TABLE 2.—*Cases of Acute Carbon Tetrachloride Poisoning Reported in the Literature*

	By Mouth	Inhalation of Fumes	Total
Numbers of cases	42	99	141
Clinical symptoms of renal damage	6	27	33
History of alcoholism	4	9	13
Fatal cases	21	18	39
Autopsy reports	19	6	25
Anatomic evidence of renal damage	12	5	17

that it played a role in some of the cases. In this connection case 3 is interesting because the co-worker of the patient, a teetotaler, had been working in the same room and had been exposed to the vapors of carbon tetrachloride for the same length of time. Although he felt the effect of the exposure and suffered from headache and gastrointestinal distress, he recovered quickly after breathing fresh air. The role of alcoholism in carbon tetrachloride poisoning has been pointed out repeatedly and has been discussed by Lamson, Minot and Robbins.[6] According to their view, alcohol either effects a greater absorption from the gastrointestinal tract or causes greater penetration into the liver. The mechanism of its influence in carbon tetrachloride poisoning by inhalation is obscure, but its effect cannot be denied. The reduction of the glycogen store in the hepatic cells of alcoholic addicts may have some importance in the greater susceptibility to carbon tetrachloride poisoning. On the other hand, there have been many instances in which carbon tetrachloride poisoning did not depend on alcoholism.

The transient mild polycythemia which has repeatedly been observed [40] and which was present in all 3 cases presented here is probably due to

the hemoconcentration after repeated vomiting; in cases of prolonged involvement it may be followed by anemia, depending on the degree of damage to the liver.

The fall in the fibrinogen content of the blood observed in cases of carbon tetrachloride poisoning [41] explains the hemorrhagic diathesis, which is a common clinical symptom and which was observed in case 3. According to Lamson, Minot and Robbins,[39] hemorrhages may be uncontrollable when both the calcium ion and the fibrinogen content of the blood are low. In this respect cholemia is of importance because of the precipitation of calcium by bile. If the calcium reserve is low, tetany, tremors and convulsions may occur. In case 2 such a picture was presented.

The plasma lipid content was determined only in case 2 (table 1). During the acute phase of the disease the total lipid content was found to be high, owing to the increase in neutral fats, while the values for phospholipids and cholesterol were within normal limits. The presence of an increased amount of neutral fat in the serum is interesting in connection with the history that the patient drank a glass of milk just after being exposed to vapors of carbon tetrachloride. It is conceivable that that the carbon tetrachloride, being an excellent fat solvent, carried more fat into the serum than would ordinarily be present. The carbon tetrachloride was then excreted through the lungs and kidneys, leaving an excess of fat in the serum. In this respect the case is similar to one described by McMahon and Weiss,[7] that of a man who drank carbon tetrachloride in milk and suffered from fat embolism. Butsch [18] also described a high lipid content in his case. Low values for plasma lipids in carbon tetrachloride poisoning were described by Lehnherr.[42]

The serum phosphatase content was moderately increased, as is often the case when the liver is damaged.

Contrary to the findings of Robbins [43] that carbon tetrachloride is not excreted by the kidneys but only through the lungs in dogs, one must assume that the chemical is at least partly excreted by the kidneys in human beings, in order to explain the renal lesions. However, in human beings with carbon tetrachloride poisoning there is probably also partial excretion through the lungs, which explains the susceptibility of this organ to subsequent infection, as seen in cases 2 and 3.

Minot and Cutler [44] found retention of guanidine in the blood of animals with carbon tetrachloride poisoning and pointed out the similarity between carbon tetrachloride and guanidine poisoning.

Much experimental work (Phelps and Hu,[2] Mauro [11] and others mentioned in the last part of the bibliography) on carbon tetrachloride poisoning has been done with laboratory animals, especially dogs, mainly with regard to hepatic damage and the development of cirrhosis. Since dogs do not excrete carbon tetrachloride through the kidneys,[43] no renal

lesions of consequence have been reported in this animal. The only reference regarding renal lesions in dogs was made by Gardner and his associates,[45] who reported albuminous fluid in almost every glomerular space and some cloudy swelling of the cells of the convoluted tubules. The statement made by Mayer and Pessôa [46] that fatty changes develop in epithelial cells of the convoluted tubules and Henle's loops after the administration of carbon tetrachloride to dogs was contradicted by Schultz and Marx,[47] who found fatty changes in these structures to be a normal feature in this animal.

Although Hall and Shillinger [48] conducted experiments with carbon tetrachloride on cats, they made no mention of renal lesions in their report. Chandler and Chopra,[49] on the other hand, described renal lesions in kittens and cats due to carbon tetrachloride and stated that the renal rather than the hepatic damage was the actual cause of death of their experimental animals. These authors concluded that the susceptibility of this organ in cats accounts for the much greater toxicity of carbon tetrachloride for cats than for dogs. The authors described lesions in the kidneys which were similar to those seen in human beings: degeneration and frequently necrosis of convoluted tubules, with desquamation of lining cells, especially of Henle's loops, infiltration of the capsule of Bowman with blood, and swelling of the glomerular epithelium as well as dilatation of vessels. The urine of these animals always contained albumin and frequently blood.

Mauro [11] conducted inhalation experiments with carbon tetrachloride on rabbits and described cloudy swelling and desquamation of the epithelial cells of the convoluted tubules and of the descending loops of Henle.

An excellent survey of the clinical and pathologic features of acute and chronic intoxication due to carbon tetrachloride in human beings has been given by Smyth [32] and by Smyth, Smyth and Carpenter,[50] who also described renal changes in experimental animals (rats, monkeys and guinea pigs), characterized by swelling, degeneration, necrosis and desquamation of the epithelial cells of the convoluted tubules and the presence of casts in the renal tubules.

On the basis of the work of Minot and Cutler,[44] it may be stated that the symptomatic treatment of carbon tetrachloride poisoning consists of giving calcium carbonate or lactate, dextrose intravenously and infusions of saline or Ringer's solution. Cases of carbon tetrachloride poisoning in which the patients responded to such symptomatic treatment have been reported by Franco,[36] Heyl [37] and others. If carbon tetrachloride is to be given by mouth, alcohol and a fatty diet should be avoided. The administration of carbon tetrachloride is contraindicated in all cases of intestinal obstruction. A high carbohydrate diet is recommended, and the treatment is followed by the administration of saline

cathartic. Recently Neale [51] reported the protective action of monosodium-2,6-dioxypurine (sodium xanthine) and sodium guanine in experimental carbon tetrachloride poisoning.

CONCLUSIONS

In addition to hepatic damage, carbon tetrachloride poisoning sometimes causes alarming renal symptoms, such as oliguria or anuria, nitrogen retention and subsequent hypertension; the urine contains albumin, white blood cells, red blood cells, casts and bile.

The anatomic basis for the clinical renal symptoms is nephrosis characterized by distention of the spaces of Bowman with albuminous precipitate, with swelling of the lining cells, swelling and vacuolation of the cells of the proximal convoluted tubules, degeneration and necrosis of the cells of the distal convoluted tubules and those of the loops of Henle, with desquamation, and by the presence of granular, hyaline and cellular casts in the tubules, with plugging of their lumens. Concretions are present whose nature and significance are obscure.

Various clinical and pathologic features of carbon tetrachloride poisoning are discussed.

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Progress in Internal Medicine

LIVER AND BILIARY TRACT

A REVIEW FOR 1938

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NEW YORK

Previous reviews [1] in this series have summarized the clinical and experimental studies concerning the physiology of the gallbladder and biliary tract. The present day treatment and medical management of cholecystitis are based on these physiologic concepts. While many clinical papers have appeared during the past year, the majority have been in accord with these ideas and so do not require specific reference at present. The treatment of hepatic disease was summarized by Greene, Handelsman and Babey [1c] in 1937 and by Snell [2] and Boyce [3] in 1938 and 1939. Reference may be made to these papers for details. At present we wish to summarize recent publications dealing with the etiology of cholelithiasis and certain of the newer developments within the larger field.

ETIOLOGY OF GALLSTONES

Since the time of Naunyn a mass of clinical and experimental data dealing with gallstones has been accumulated, and a multitude of theories have been propounded to explain the causation of gallstones.

This material has recently been reviewed by Carter, Greene, Twiss and Hotz,[4] who have emphasized the multiplicity and complexity of the

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1. (*a*) Greene, C. H.; Bercovitz, Z., and Hanssen, E. C.: Liver and Biliary Tract: Review of the Literature of 1933 and 1934, Arch. Int. Med. **55**:681 (April) 1935. (*b*) Greene, C. H.: Liver and Biliary Tract: Review of Certain Recent Contributions, ibid. **57**:1039 (May) 1936. (*c*) Greene, C. H.; Handelsman, M. B., and Babey, A. M.: Liver and Biliary Tract: A Review for 1936, ibid. **59**:724 (April) 1937. (*d*) Greene, C. H.; Plotz, M., and Localio, S. A.: Liver and Biliary Tract: A Review for 1937, ibid. **61**:655 (April) 1938.

2. Snell, A. M.: The Treatment of Liver Disease, Ann. Int. Med. **12**:592, 1938.

3. Boyce, F. F.: Hepatic and Biliary Tract Disease: A Review of Recent Significant Advances, Ann. Surg. **109**:351, 1939.

4. Carter, R. F.; Greene, C. H.; Twiss, J. R., and Hotz, R.: Etiology of Gall Stones, Am. J. M. Sc., to be published.

factors which apparently enter into the formation of biliary calculi. In addition, there are several varieties of gallstones. These authors have suggested that while the factors affecting the formation of gallstones are multiple, they may be divided into two groups. The first group is related to changes in the hepatic bile, while the second is related to changes taking place directly in the gallbladder or bile ducts. These authors have reported on a series of 239 cases, with complete preoperative and postoperative studies, and have investigated the applicability of the various theories in explaining the origin of the stones.

The metabolic theory assumes that disturbances in metabolism so change the hepatic bile as to predispose to the formation of concrements. Giffin,[5] in particular, has emphasized the frequency of gallstones (58 per cent) in adults with congenital hemolytic jaundice. These characteristically are hard, brown or black pigment stones consisting of bilirubin and calcium bilirubinate. They are apparently related to the pleocholia or excessive excretion of bile pigment in this condition. Greene and Snell[6] found experimentally that an augmented rate of excretion of pigment in the bile was brought about primarily by an increase in the concentration rather than by an increase in the volume of the bile. This pleocholia therefore may well predispose to the deposition of this particular form of calculus.

The metabolic theory is usually restricted to the formation of cholesterol stones. As advocated by Chauffard and his co-workers,[7] it assumes a correlation between the concentration of cholsterol in the blood and that in the bile, so maintained that an elevated value for cholesterol in the blood is a predisposing factor in the formation of gallstones. The clinical experience of Chauffard, Moynihan,[8] Hansen,[9] Dewey[10] and others seemingly has substantiated this belief. The observation of an increased concentration of cholesterol in both blood and bile during pregnancy, the frequent onset of clinical symptoms during or immediately after pregnancy and the increased incidence of gallstones in

5. Giffin, H. Z.: Hemolytic Jaundice: A Review of Seventeen Cases, Surg., Gynec. & Obst. **25**:152, 1917.

6. Greene, C. H., and Snell, A. M.: Studies in the Metabolism of the Bile: II. The Sequence of Changes in the Blood and Bile Following the Intravenous Injection of Bile or Its Constituents, J. Biol. Chem. **78**:691, 1928.

7. Chauffard, A.; LaRoche, G., and Grigaut, A.: Le taux de la cholestérinémie chez les hépatiques, Compt. rend. Soc. de biol. **70**:20, 1911. Chauffard, A.: Leçons sur la lithiase biliaire, Paris, Masson & Cie, 1914.

8. Moynihan, B.: Some Aspects of Cholelithiasis, Brit. M. J. **1**:393, 1925.

9. Hansen, S.: Die Bedeutung des Cholesterins für die Bildung von Gallensteinen durch experimentelle Untersuchungen beleuchtet, Acta chir. Scandinav. **62**: 383, 1927.

10. Dewey, K.: Experimental Hypercholesterolemia, Arch. Int. Med. **17**:757 (June) 1916.

women as compared to that in men have all been factors in the acceptance of this theory. Feeding experiments with animals, using diets rich in cholesterol, have demonstrated that the cholesterol content of the blood can be increased markedly by each feeding. This view has received added confirmation by the work of Wilensky [11] and Rothschild and Wilensky.[12] Walsh;[13] Walsh and Ivy;[14] Andrews, Hrdina and Dostal;[15] Riegel, Ravdin and Rose;[16] Patey,[17] and many others, however, could find no such definite relation between the cholesterol content of the blood and that of either the hepatic or the gallbladder bile, either in patients or in experimental animals. Carter, Greene, Twiss and Hotz [4] therefore concluded that there is no direct relation between the cholesterol content of the blood and the formation of gallstones.

The bile salts in hepatic bile are the specific secretion of the hepatic cells, and numerous investigators, notably Stadelmann;[18] Whipple;[19] Ivy;[20] Doubilet;[21] Greene, Walters and Fredrickson,[22] and others, have shown that this excretion in the bile is an extremely sensitive index to the functional activity of the hepatic parenchyma. The bile salts also have a role in keeping the cholesterol of the bile in solution. Changes in the functional activity of the liver from hepatitis, suppression of secretion

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11. Wilensky, A. O.: Hypercholesteremia, Surg., Gynec. & Obst. **38**:163, 1924.

12. Rothschild, M. A., and Wilensky, A. O.: Studies in Cholelithiasis: I. The Disturbances of the Cholesterin Metabolism as a Factor in Gall Stone Formation, Am. J. M. Sc. **156**:239, 1918; II. The Clinical Relationships of Cholesterinemia to the Pathological Process, ibid. **156**:404, 1918.

13. Walsh, E. L.: The Etiology of Gallbladder Calculi, Arch. Path. **15**: 698 (May) 1933.

14. Walsh, E. L., and Ivy, A. C.: Observations on the Etiology of Gall Stones, Ann. Int. Med. **4**:134, 1930.

15. Andrews, E.; Hrdina, L., and Dostal, L. E.: Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, Arch. Surg. **25**:1081 (Dec.) 1932.

16. Riegel, C.; Ravdin, I. S., and Rose, H. J.: Studies of Gallbladder Function: XV. Cholesterol in Human Liver Bile, J. Clin. Investigation **16**:67, 1937.

17. Patey, D. H.: Modern Views on Mechanism of Formation of Gall Stones, Brit. M. J. **1**:866, 1933.

18. Stadelmann, E.: Der Icterus und seine verschiedenen Formen, Stuttgart, Ferdinand Enke, 1891.

19. Whipple, G. H.: Origin and Significance of Constituents of the Bile, Physiol. Rev. **2**:440, 1922.

20. Ivy, A. C.: Factors Concerned in the Evacuation of the Gall Bladder, Medicine **11**:345, 1932.

21. Doubilet, H.: Hepatic Excretion in Man of the Various Bile Acids Following Their Oral Administration, Proc. Soc. Exper. Biol. & Med. **36**:50, 1937.

22. Greene, C. H.; Walters, W., and Fredrickson, C. H.: The Composition of the Bile Following the Relief of Biliary Obstruction, J. Clin. Investigation **9**: 295, 1930.

or metabolic disturbances may so change the concentration of bile salts in the hepatic bile as to favor the precipitation of cholesterol. The importance of this ratio of bile salts to cholesterol in the formation of gallstones will be discussed presently.

The excretion of bacteria, bile thrombi or abnormal toxic products, due to hepatic damage, and other organic changes in the liver and its secretion have repeatedly been suggested as forming the nuclei for stones. Crile [23] believes that energy changes in the body, affecting the liver and causing abnormality of the bile, result in the formation of stones and that these in turn cause the infection frequently seen in calculous gallbladders. He stated: "Our thesis is that the chemical and physical basis of gall stones is laid by changes in the secretion of the biologically active liver cells and not by changes in the sac that holds and concentrates the bile and performs no other function."

Rous, Drury and McMaster [24] have demonstrated the formation of stones without any evidence of stasis, infection or changes in the composition of the blood. They concluded from this experimental work that stones may form from altered hepatic secretion. Rovsing [25] came to a similar conclusion.

Attempts to show a relation between the intake of fluids and the volume of bile secreted by the liver have been unsuccessful. Of seemingly greater importance are the changes occurring in bile during its passage through the bile ducts and gallbladder. It is here that the controversy concerning the physiology of the gallbladder becomes of major importance in evaluating theories concerning the formation of gallstones. The question is: Does the normal gallbladder absorb cholesterol, as is maintained by Policard,[26] Whitaker,[27] Mentzer,[28] Boyd,[29] Halpert,[30]

23. Crile, G.: Energy Background of Genesis of Gall Stones and of Prevention of Immediate Postoperative Shock and of Later Digestive Disturbances, Surg., Gynec. & Obst. **60**:818, 1935.

24. Rous, P.; Drury, D. R., and McMaster, P. D.: Observations on Some Causes of Gall Stone Formation: II. On Certain Special Nuclei of Deposition in Experimental Cholelithiasis, J. Exper. Med. **39**:97, 1924.

25. Rovsing, T.: Gall Stones the Cause, Not the Result, of Infection, Acta chir. Scandinav. **56**:103, 1923.

26. Policard, A.: Sur quelques données histophysiologiques concernant les mécanismes fonctionnels et pathologiques de la vésicule et des voies biliaires, Lyon chir. **19**:799, 1922.

27. Whitaker, L. R.: The Relation of Biliary Dysfunction to Lithiasis, New York State J. Med. **34**:221, 1934.

28. Mentzer, S. H.: The Pathogenesis of Biliary Calculi, Arch. Surg. **14**:14 (Jan., pt. 1) 1927.

29. Boyd, W.: Studies in Gall Bladder Pathology, Brit. J. Surg. **10**:337, 1923.

30. Halpert, B.: The Gallbladder in the Light of Recent Investigation, Arch. Surg. **19**:1037 (Dec., pt. 1) 1929.

Sweet [31] and others; does it secrete cholesterol, as has been contended by Elman and Graham [32] and as was originally contended by Naunyn,[33] or does it normally only concentrate cholesterol, as indicated by the observations and experimental data of Ravdin and Johnson,[34] Walsh, and Andrews, Schoenheimer and Hrdina [35]? Lichtwitz,[36] in 1914, further complicated the question by suggesting that cholesterol saturation of the plicae of the gallbladder, by absorption from the bile, and their subsequent dehiscence formed the nuclei for "metabolic stones." Though this concept has been supported more recently by Gosset, Bertrand and Lœwy,[37] it has been denied by Illingworth [38] and Mackey.[39]

It is generally agreed that the gallbladder extracts water, sodium chloride and other inorganic salts from the hepatic bile, concentrating it from seven to ten times (Ravdin and Johnson [34] and others). It appears from clinical and experimental studies that while the mucosa of the gallbladder may absorb bile salts or cholesterol from the bile, this does not occur under normal circumstances. In the presence of an inflammation, when the mucosa is edematous, Dostal and Andrews [40] have shown that bile salts are rapidly absorbed by the wall of the gallbladder. Clinically this is seen most readily in cases of hydrops of the gallbladder. Another explanation, advanced by Rous and McMaster,[41] is that bile, including cholesterol and bile salts, is replaced by mucus which is a specific

31. Sweet, J. E.: The Formation of Gallstones, Am. J. Surg. **40**:162, 1938.

32. Elman, R., and Graham, E. A.: Pathogenesis of "Strawberry" Gallbladder (Cholesterosis of the Gallbladder), Arch. Surg. **24**:14 (Jan.) 1932.

33. Naunyn, B.: Klinik der Cholelithiasis, Leipzig, F. C. W. Vogel, 1892; A Treatise on Cholelithiasis, translated by A. E. Garrod, London, New Sydenham Society, 1896; Die Gallensteine: Ihre Entstehung und ihr Bau, Jena, Gustav Fischer, 1921.

34. Ravdin, I. S., and Johnson, C. G.: The Gall Bladder: Recent Advances as Applied to Treatment, Pennsylvania M. J. **35**:357, 1932.

35. Andrews, E.; Schoenheimer, R., and Hrdina, L.: Etiology of Gallstones: Chemical Factors and Role of the Gallbladder, Arch. Surg. **25**:796 (Oct.) 1932.

36. Lichtwitz, L.: Ueber die Bildung der Harn und Gallensteine, Ergebn. d. inn. Med. u. Kinderh. **13**:1, 1914.

37. Gosset, A.; Bertrand, I., and Lœwy, G.: La vésicule fraise, Progrès méd. **44**:1792, 1928.

38. Illingworth, C. F. W.: Cholesterosis of the Gall Bladder: A Clinical and Experimental Study, Brit. J. Surg. **17**:203, 1929.

39. Mackey, A.: Cholesterosis of the Gall Bladder, Brit. J. Surg. **24**:570, 1937.

40. Dostal, L. E., and Andrews, E.: Etiology of Gallstones: Effect of Diet on the Bile Salt-Cholesterol Ratio, Arch. Surg. **26**:258 (Feb.) 1933.

41. Rous, P.; Drury, D. R., and McMaster, P. D.: Observations on Some Causes of Gall Stone Formation: II. On Certain Special Nuclei of Deposition in Experimental Cholelithiasis, J. Exper. Med. **39**:97, 1924.

response of the mucosa of the gallbladder. Aronsohn and Andrews [42] have demonstrated that chemical cholecystitis may be set up by a high concentration of bile salts in the gallbladder and possibly in the blood stream. How then can one account for the concentration of cholesterol which may be found in gallbladder bile—100 to 2,000 mg. per hundred cubic centimeters? The hepatic bile contains little cholesterol, and yet ten to a hundred times this concentration is often seen in the gallbladder at operation; whereas the bile salt concentration is seldom above seven to ten times the concentration in the hepatic bile. While this finding may be cited as evidence that the cholesterol is secreted by the mucosa of the gallbladder, the work of Boyd, Whitaker, Sweet, and Wilkie and Doubilet [43] opposes such an assumption.

It is agreed that some if not all of the cholesterol in the bile is in a state of colloidal solution. The studies of Wieland and Sorge [44] showed that the bile salts, particularly the salts of desoxycholic acid, form addition compounds with fatty acids or cholesterol which increase the solubility of the cholesterol. Verzár,[45] in particular, has stressed the importance of such compounds in favoring the intestinal absorption of lipoids and cholesterol. Other investigators, following Newman,[46] have stressed the importance of these compounds in keeping the cholesterol in the bile in solution and have insisted that when the ratio of bile salts to cholesterol falls below a critical level, cholesterol is precipitated out of solution. It is further assumed that such precipitation leads to the formation of cholesterol calculi.

The bile salt–cholesterol ratio may be disturbed either by hepatic damage with a changed hepatic bile or by a differential absorption of cholesterol and bile salts in the gallbladder or bile ducts. Hammarsten [47] reported the bile salt–cholesterol ratio in normal gallbladders to be 25:1. Newman, who first emphasized the importance of this ratio in

42. Aronsohn, H. G., and Andrews, E.: Experimental Cholecystitis, Surg., Gynec. & Obst. **66**:748, 1938.

43. Wilkie, A. L., and Doubilet, H.: Passage of Cholesterol Through the Mucosa of the Gallbladder, Arch. Surg. **26**:110 (Jan.) 1933.

44. Wieland, H., and Sorge, H.: Untersuchungen über die Gallensäuren, Ztschr. f. physiol. Chem. **97**:1, 1916.

45. Verzár, F., and von Kúthy, A.: Die Bedeutung der Gallensäuren für die Fettresorption (Arbeiten über Resorption), Biochem. Ztschr. **205**:369, 1929. Verzár, F.: Die Bedeutung der gepaarten Gallensäuren für die Fettresorption, ibid. **230**:451, 1931; Absorption of Fats, Nutrition Abstr. & Rev. **2**:441, 1933.

46. Newman, C.: Physiology of the Gall Bladder and Its Functional Abnormalities, Lancet **1**:785 and 896, 1933.

47. Hammersten, O.: Zur Chemie der Galle, Ergebn. d. Physiol. **4**:1, 1905; Text-Book of Physiological Chemistry, ed. 5, translated by J. A. Mandel, New York, J. Wiley & Sons, 1906.

the pathogenesis of gallstones, stated that the critical ratio for the precipitation of cholesterol is 18:1. Andrews, Schoenheimer and Hrdina have placed the critical ratio at 13:1.

Carter, Greene, Twiss and Hotz found that in their cases the bile salt–cholesterol ratio was highly variable and that the difference between the ratios in cases of calculous and of noncalculous gallbladders was not sufficient to account for the stones. Chabrol, Cottet and Cachin [48] have suggested that the bile salt–cholesterol ratio may well be disturbed by the factors causing the gallstones more frequently than it is the cause of the latter. Walsh and Ivy; Walsh, and Dolkart, Jones and Brown,[49] in exhaustive experimental studies, have shown that fatty acids have a markedly solvent action on cholesterol masses and on "mixed gallstones." They believe therefore that it is the concentration of fatty acids in the bile rather than that of bile salts that keeps the cholesterol in solution. Illingworth; Reinhold, Ferguson and Hunsberger,[50] and Weiser and Gray,[51] on the other hand, do not attach significance to the presence of fatty acids, for they were unable to demonstrate fatty acids in bile from normal gallbladders in sufficient concentration to prevent the precipitation of cholesterol.

Phemister and his associates [52] have reported that precipitates of calcium salts are formed in the gallbladder only when complete obstruction and low grade chronic inflammation are present. They believe that since cholesterol is not found in such gallbladders, the gallbladder cannot be the source of the cholesterol found in gallstones. Calcium salts, they believe, represent a specific response on the part of the wall of an inflamed gallbladder.

Reported changes in the reaction of bile have not been consistently demonstrated in calculous gallbladders. Feldman, Morrison and

48. Chabrol, E.; Cottet, J., and Cachin, M.: Recherches sur le rôle respectif du cholestérol et de l'acide cholalique dans la pathogénie de la lithiase biliaire, Ann. de méd. **42**:607, 1937.

49. Dolkart, R. E.; Jones, K. K., and Brown, C. F. G.: The Relation of the Hydrogen Ion Concentration of Bile to the Formation of Gall Stones, Am. J. Digest. Dis. & Nutrition **4**:587, 1937; Chemical Factors Concerned in the Formation of Gallstones, Arch. Int. Med. **62**:618 (Oct.) 1938.

50. Reinhold, J. G.; Ferguson, L. K., and Hunsberger, A.: Composition of the Human Gall Bladder Bile and Its Relationship to Cholelithiasis, J. Clin. Investigation **16**:367, 1937.

51. Weiser, H. B., and Gray, G. R.: Mechanism of the Formation of Pure Cholesterol Gallstones, Arch. Path. **17**:1 (Jan.) 1934.

52. Phemister, D. B.; Day, L., and Hastings, A. B.: Calcium Carbonate Gallstones and Their Experimental Production, Ann. Surg. **96**:595, 1932. Phemister, D. B.; Aronsohn, H. G., and Pepinski, R.: Variations in Cholesterol, Bile Pigment, and Calcium Salts Contents of Gallstones Formed in Gallbladder and in Bile Ducts with the Degree of Associated Obstruction, ibid. **109**:161, 1939.

Krantz,[53] reasoning from the observation that human cholesterol and "mixed gallstones" will dissolve when placed in the more acid gallbladder bile of a dog, believe that the alkaline p_H found in human hepatic bile, unchanged by the gallbladder, may be an important etiologic factor in the formation of gallstones. Reinhold, Ferguson and Hunsberger; Reinhold and Ferguson;[54] Rous,[55] and Weiser and Gray, on the other hand, did not find that the normal gallbladder bile had a higher hydrogen ion concentration than hepatic bile, nor do they believe that there is any marked change in the presence of an inflammation. Walsh reported that an acid p_H allows cholesterol to stay in solution more readily, but he ascribed this to the presence of bile acids and to fatty acids, which are known solvents of cholesterol. Dolkart, Jones and Brown found no statistically significant difference in the relative solvent action upon mixed stones of acid and of alkaline bile secured from the ox, the dog and man.

The original hypothesis of Naunyn, propounded in 1892, held that gallstones are the result of infection in the gallbladder or bile ducts. Nearly all subsequent theories have presupposed that some injury, inflammation or chemical change of the bile in the gallbladder is the initiating cause for the formation of stones. As Sir Berkeley Moynihan has stated, "The gall stone is a tombstone erected to the memory of the organism within it." The early clinical researches indicated that most gallbladders with stones were infected. Gordon-Taylor and Whitby[56] found 70 per cent infected; Moynihan found 95 per cent infected and Walton[57] found 70 per cent infected. Various recent clinical studies have shown a wide variation in the incidence of positive results of culture in cases of calculous gallbladders. Moynihan; Griffith and Kipp;[58]

53. Feldman, M.; Morrison, S., and Krantz, J. C.: Etiology of Gall Stones: Relationship of p_H of Bile to Formation and Dissolution of Gall Stones, Am. J. Digest. Dis. & Nutrition **4**:13, 1937. Feldman, M.; Morrison, S.; Carr, C. J., and Krantz, J. C.: Etiology of Gall Stones: Hydrogen Ion Concentration of Gall Bladder Bile and Its Effects upon Gall Stones, ibid. **4**:223, 1937.

54. Reinhold, J. G., and Ferguson, L. K.: Reaction of Human Bile and Its Relationship to Gall Stone Formation, J. Exper. Med. **49**:681, 1929.

55. Rous, P.: Physiological Factors in the Genesis of Gall Stones, Proc. Inst. Med. Chicago **7**:33, 1928.

56. Gordon-Taylor, G., and Whitby, L. E. H.: A Bacteriological Study of Fifty Cases of Cholecystectomy with Special Reference to Anaerobic Infections, Brit. J. Surg. **18**:78, 1930.

57. Walton, J.: The Formation and Treatment of Calculi in the Biliary Ducts and Gall Bladder, Surg., Gynec. & Obst. **64**:257 1937.

58. Griffith, J. P., and Kipp, H. A.: Remarks on the Etiology and Treatment of Cholecystitis, Pennsylvania M. J. **35**:362, 1932.

Patey; Walton; Albeaux-Fernet,[59] and Walters,[60] as well as many others, are certain, from a clinical point of view, that infection of the gallbladder is a basic cause for the formation of stones, infection causing changes in the mucosa with resulting functional disturbances, stasis and colloidal changes favoring precipitation. All are in agreement that pure cholesterol stones are metabolic in origin and differ thus from mixed or common gallstones. Potter and Mann;[61] Illingworth; Ravdin and Johnson, and Fürth[62] have reached the same general conclusion after animal experimentation as well as clinical studies. Illingworth believes that the Lichtwitz theory of electropositive and electronegative charges, with the inflammatory exudate acting as an electronegative substance, may explain the "trigger mechanism" which causes the cholesterol to precipitate.

Aschoff and Bacmeister,[63] Rovsing and Crile, after both clinical and experimental studies, on the other hand, believe that the infection is the consequence and not the cause of gallstones. MacCarty[64] made a statistical study of 21,523 gallbladders but was unable to determine which was the prior factor, whereas Walters, and Ravdin and Johnson believe either may be the initial condition. Carter, Greene, Twiss and Hotz have pointed out that it is debatable whether this question can be answered by clinical research alone. In only 33 per cent of the cases which they classified as cases of "early cholecystitis" with or without stones was there either bacteriologic or pathologic evidence of inflammation or infection. In 24 cases gallstones were present, but there was no pathologic or bacteriologic evidence of inflammation or infection. This group of cases they considered as evidence that infection is not necessary for the formation of stones and as presumptive evidence that the formation of stones may precede infection of the gallbladder.

The assumption of Aschoff and Bacmeister that infection or the products of infection are not the cause of stones arose from their experimental and clinical studies on the precipitation of cholesterol in the presence of stasis within the gallbladder. They maintained that this stasis, regardless of the cause, favored changes in solubility due to over-

59. Albeaux-Fernet, M.: Les hypothèses pathogéniques de la lithiase biliaire, Gaz. méd. de France (supp. Gastro-enterol.) [**43**]:3, 1936.

60. Walters, W.: Pathological Physiology of Stone in the Common Duct: Clinical and Surgical Significance, Surg., Gynec. & Obst. **63**:417, 1936.

61. Potter, J. C., and Mann, F. C.: Pressure Changes in the Biliary Tract, Am. J. M. Sc. **171**:202, 1926.

62. Fürth, O.: Pathologische Physiologie der Steinbildung, Wien. klin. Wchnschr. **50**:68, 1937.

63. Aschoff, L., and Bacmeister, A.: Die Cholelithiasis, Jena, Gustav Fischer, 1909. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924.

64. MacCarty, W. C.: The Gallbladder and Its Diseases, Proc. Staff Meet., Mayo Clin. **11**:805, 1936.

concentration of the cholesterol with resultant precipitation. The precipitated cholesterol was the nucleus of stones. The fact that many pathologic conditions, as well as some that are neurogenic in origin, result in biliary stasis and an increased concentration of the bile within the gallbladder has been established by Westphal;[65] Ivy; Whitaker, and Greene, Twiss and Carter.[66] McMaster and Elman,[67] Boyden,[68] Whitaker, and Ravdin and Johnson could demonstrate no definite reciprocal relation between the sphincter of Oddi and the gallbladder of dogs. According to Berg and Jobling,[69] Ivy and Mentzer, there is much indirect evidence that such a relation does exist.

Whitaker has demonstrated the formation of pseudostones in the gallbladder of dogs by inducing stasis in the absence of infection or hepatic damage. Mentzer, von Babarczy [70] and Halpert have also made a strong case for stasis. Ravdin and Johnson, Walters, Walsh, Moore [71] and Rous have shown that stasis is at least an accessory factor in stone formation. Copher and Illingworth [72] were unable to reproduce Whitaker's experiments and so agree with Pavel,[73] Fürth and many others that stasis probably is not a cause for the formation of gallstones.

The observation that pure cholesterol stones may crystallize according to the laws of colloids has led to the colloidal theory of stone formation,

65. Westphal, K.: Muskelfunktion, Nervensystem und Pathologie der Gallenwege, Ztschr. f. klin. Med. **96**:22, 1933; Die Bewegungs- und Resorptionsstörungen an den Gallenwegen und ihre Gefahren, Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. 44, 1932, p. 354.

66. Greene, C. H.; Twiss, J. R., and Carter, R. F.: Biliary Stasis, Am. J. Digest. Dis. & Nutrition **3**:622, 1936.

67. McMaster, P. D., and Elman, R.: On the Expulsion of Bile by the Gall Bladder and a Reciprocal Relationship with the Sphincter Activity, J. Exper. Med. **44**:173, 1926.

68. Boyden, E. A.: Sphincter of Oddi in Man and Certain Representative Mammals, Surgery **1**:25, 1937.

69. Berg, B. N., and Jobling, J. W.: The Effect of Division and Transplantation of the Common Duct upon the Gall-Bladder Function, Proc. Soc. Exper. Biol. & Med. **24**:434, 1927. Berg, B. N.: Gall Bladder Function After Divison of the Common Duct, Surg., Gynec. & Obst. **46**:464, 1927.

70. von Babarczy, M.: Die Bedeutung des Cholesterins in der Diätetik der Cholecystopathien, Ztschr. f. klin. Med. **133**:656, 1938.

71. Moore, S. W.: Intramural Formation of Gallstones, Arch. Surg. **34**:410 (March) 1937.

72. Copher, G. H., and Illingworth, C. F. W.: Experimental Study of the Factor of Biliary Stasis in the Production of Gall Stones, Surg., Gynec. & Obst. **46**:658, 1928.

73. Pavel, I.: Du rôle peu important de la stase dans la pathogénie de la lithiase biliaire (avec une critique de la dyskinésie et quelques considérations thérapeutiques), Presse méd. **43**:1565, 1935.

supported extensively by Sweet,[74] Weiser and Gray, and Schade.[75] Sweet has maintained that "under normal conditions, whatever passes into the gallbladder through the cystic duct, never passes out again through the cystic duct." He found synthetic stones made from gelatin, chromates and silver nitrate to be structurally similar to the cholesterol stones in the human gallbladder. The Liesegang phenomena, with rhythmic precipitation of calcium and pigment, he thinks, explain the laminated appearance on section of cholesterol and mixed gallstones. Phemister, on the other hand, has insisted that the deposition of calcium is evidence of inflammatory changes in the wall of the gallbladder. When a gallstone consists of a central nucleus of cholesterol with several rings of calcium and pigment around the periphery, Phemister and others have insisted that this structure is evidence for the occurrence of successive attacks of obstruction and active cholecystitis in a gallbladder which initially contained a pure cholesterol stone of metabolic origin. At present these opposing views of Phemister and Sweet are irreconcilable.

Pancreatic ferments have been found in many calculous gallbladders removed at operation, and it has been assumed that the ferments were regurgitated up the common and cystic ducts into the gallbladder. Sweet, Crile, and Wolfer [76] believe this may be a factor leading to the precipitation of cholesterol. Colp, Gerber and Doubilet [77] believe such a reflux was the cause of severe acute cholecystitis seen in 3 cases which they reported. Aronsohn and Andrews [78] were able markedly to change the bile salt–cholesterol ratio in the gallbladders of dogs by injecting pancreatic fluid into them. Carter, Greene, Twiss and Hotz have suggested that the common finding of pancreatic ferments in gallbladders removed at operation warrants further investigation, for their data were inconclusive. This is particularly important if the observation of

74. Sweet, J. E.: (*a*) The Liesegang Phenomenon in Gall Stones, in Colloid Symposium Annual: Papers Presented at the Seventh Symposium on Colloid Chemistry at Johns Hopkins University in June 1929, New York, 1930, p. 249; (*b*) Formation of Calculi, Ann. Surg. **103**:67, 1936.

75. Schade, H.: Zur Entstehung der Harnsteine und ähnlicher konzentrisch geschichteter Steine organischen und anorganischen Ursprungs, Ztschr. f. Chem. u. Indust. d. Kolloide **4**:175, 1909; cited by Sweet.[74b]

76. Wolfer, J. A.: Further Evidence That Pancreatic Juice Reflux May Be the Etiologic Factor in Gallbladder Disease, Ann. Surg. **109**:187, 1939.

77. Colp, R.; Gerber, L. C., and Doubilet, H.: Acute Cholecystitis Associated with Pancreatic Reflux, Ann. Surg. **103**:67, 1936.

78. Aronsohn, H. G., and Andrews, E.: Experimental Cholecystitis, Surg., Gynec. & Obst. **66**:748, 1938.

Mehnen [79] is confirmed that the frequency of gallstones is greatest in those cases in which the anatomic structure of the papilla of Vater favors the regurgitation of pancreatic juice into the gallbladder.

Carter, Greene, Twiss and Hotz have pointed out that their study served to emphasize the difficulty of determining the causation and pathogenesis of gallstones solely by study of the patient at the time of operation. If the deposition of a calculus depends on the concomitant action of several different factors, then the period of calculous formation may be limited in extent, and a study of the patient one to twenty-five years later will fail to present the true picture of the conditions determining the deposition of the stone. It must also be recognized that the different types of gallstones may differ as to causation. When the various theoretic factors advanced as possible causes of gallstones were studied, these authors found no single factor or combination of factors which satisfactorily explained the origin of gallstones. In their series of cases, stasis was the only one of the factors considered that could be demonstrated in 25 per cent of the cases of gallstones. They consider this presumptive evidence that stasis is of importance in the formation of gallstones, but they have pointed out that other unknown factors must also be in operation, for stasis was found in the majority of the noncalculous gallbladders as well.

SERUM PHOSPHATASE IN JAUNDICE

In the review for 1937 [1d] reference was made to a series of papers by Thannhauser and his associates [80] reporting that ascorbic acid activates the serum phosphatase. Theoretic conclusions regarding the cause and significance of the increase in serum phosphatase in jaundice were drawn on the basis of these observations. During the past year,

79. Mehnen, H.: Die Bedeutung der Mündungsverhältnisse von Gallen- und Pankreasgang für die Entstehung der Gallensteine, Arch. f. klin. Chir. **192**:559, 1938.

80. Thannhauser, S. J.; Reichel, M., and Grattan, J. F.: Studies on Serum Phosphatase Activity: I. Ascorbic Acid Activation on Serum Phosphatase, J. Biol. Chem. **121**:697, 1937. Thannhauser, S. J.; Reichel, M.; Grattan, J. F., and Maddock, S.: II. The Effect of Experimental Total Biliary Obstruction on the Serum Phosphatase Activation in Dogs and Cats, ibid. **121**:709, 1937; III. The Effect of Complete Biliary Fistula on Phosphatase Activation in Dogs and Cats, ibid. **121**: 697, 1937; IV. The Deactivating Effect of Thiol Compounds and Bile Acids on Serum Phosphatase in Vitro and in Vivo, ibid. **121**:720, 1937; V. Studies Concerning Increased Serum Phosphatase Values in Disease, ibid. **121**:727, 1937. Maddock, S.; Thannhauser, S. J.; Reichel, M., and Grattan, J. F.: A New Conception of Serum Phosphatase: A Review of Experimental Work, New England J. Med. **218**:166, 1938.

King and Delory [81] reported that they were unable to confirm Thannhauser's basic observations regarding the effect of ascorbic acid on phosphatase activity. Thannhauser, Reichel and Grattan [82] then repeated their earlier work and found that when solutions of ascorbic acid and beta glycerophosphate were allowed to stand, the glycerophosphate was hydrolyzed. In their earlier experiments this spontaneous hydrolysis was misinterpreted as evidence of activation of the phosphatase. Thannhauser, Reichel and Grattan therefore abandoned their theory that ascorbic acid activates the serum phosphatase.

Thannhauser, Reichel, Grattan and Maddock [83] have not abandoned their interpretation of the cause for the increased serum phosphatase value in jaundice. They have made reference to the observation of Freeman and Chen [84] that when a normal dog is given a transfusion of normal blood, there is no change in the serum phosphatase level; when blood from a dog with obstructive jaundice is given, the serum phosphatase level of the recipient invariably rises to a high level and remains unchanged during the course of the acute experiment. In some cases it did not return to normal by the eighth day after the transfusion. Thannhauser and his associates [83] also reported experiments in which serum from a dog with jaundice was mixed with normal serum in vitro. The phosphatase activity of the mixture was greater than that calculated from the phosphatase activity of the original serums. They therefore reiterated their original contention that in cases of jaundice the serum contains a substance that will activate the phosphatase in normal serum.

Clinical experience in the use of the serum phosphatase value in the differential diagnosis of jaundice, as reported by Giordano, Wilhelm and Prestrud,[85] confirms the previous contention of Greene, Shattuck and Kaplowitz [86] that this is not a dependable diagnostic procedure.

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81. King, E. J., and Delory, G. E.: Ascorbic Acid and Phosphatase Activity, Biochem. J. **32**:1157, 1938.

82. Thannhauser, S. J.; Reichel, M., and Grattan, J. F.: The Effect of Ascorbic Acid on β-Glycerophosphate, Biochem. J. **32**:1163, 1938.

83. Thannhauser, S. J.; Reichel, M.; Grattan, J. F., and Maddock, S. J.: Studies on Serum Phosphatase Activity: VI. The Influence of Sera with High Phosphatase Activity on Normal Sera, J. Biol. Chem. **124**:631, 1938.

84. Freeman, S., and Chen, Y. P.: The Effect of Jaundiced Blood upon Normal Dogs, with Special Reference to the Serum Phosphatase, J. Biol. Chem. **123**:239, 1938.

85. Giordano, A. S.; Wilhelm, A., and Prestrud, M. C.: The Serum Phosphatase in the Differential Diagnosis of Obstructive Jaundice, Am. J. Clin. Path. **9**:226, 1939.

86. Greene, C. H.; Shattuck, H. F., and Kaplowitz, L.: The Phosphatase Content of the Blood Serum in Jaundice, J. Clin. Investigation **13**:1079, 1934.

SULFANILAMIDE AND THE LIVER

The past two years have witnessed the introduction of a new chemotherapeutic agent for the treatment of hemolytic streptococcic infection. Sulfanilamide is now accepted by the medical profession, and its therapeutic value is generally recognized. The clinical literature dealing with its use is voluminous and will not be reviewed here, as this has been done in part by Colebrook and Kenny;[87] Colebrook, Buttle and O'Meara;[88] Long and Bliss;[89] Marshall, Emerson and Cutting;[90] Ottenberg,[91] and many others.

The earlier clinical and experimental reports indicated that exceedingly large doses were necessary to produce toxic effects in either animals or man. It was a surprise, therefore, in September and October 1937 when a series of deaths supposedly due to poisoning by sulfanilamide were reported.[92] There were over a hundred finally reported, which were traced to poisoning by elixir of sulfanilamide (Massengill).[93] The patients complained of nausea, abdominal cramps, dizziness, malaise and vomiting. This was followed by oliguria and anuria. The patients became drowsy and had slight jaundice in some instances. They became progressively comatose and died in uremic coma.[94]

87. Colebrook, L., and Kenny, M.: Treatment of Human Puerperal Infections and of Experimental Infections in Mice with Prontosil, Lancet **1**:1279, 1936.

88. Colebrook, L.; Buttle, G. H. A., and O'Meara, R. A. Q.: Mode of Action of *p*-Aminobenzenesulphonamide and Prontosil in Hemolytic Streptococcal Infections, Lancet **2**:1323, 1936.

89. Long, P. H., and Bliss, E. A.: Para-Amino-Benzene-Sulfonamide and Its Derivatives: Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcic Infection; Preliminary Report, J. A. M. A. **108**:32 (Jan. 2) 1937; Clinical Use of Sulfanilamide, Ann. Int. Med. **11**:575, 1937.

90. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Para-aminobenzenesulfonamide: Absorption and Excretion; Method of Determination in Urine and Blood, J. A. M. A. **108**:953 (March 20) 1937.

91. Ottenberg, R.: The Treatment of Hemolytic Streptococcus Infections and the Newer Applications of Sulphanilamide, Bull. New York Acad. Med. **14**:453, 1938.

92. Elixir of Sulfanilamide-Massengill: II, report of the Chemical Laboratory, J. A. M. A. **109**:1724 (Nov. 20) 1937. Deaths Due to Elixir of Sulfanilamide-Massengill: Report of Secretary of Agriculture Submitted in Response to House Resolution 352 of Nov. 18, 1937, and Senate Resolution 194 of Nov. 16, 1937, ibid. **109**:1985 (Dec. 11) 1937.

93. Deaths Following Elixir of Sulfanilamide-Massengill, editorial, J. A. M. A. **109**:1367 (Oct. 23) 1937.

94. Ruprecht, H. A., and Nelson, I. A.: Clinical and Pathologic Observations, J. A. M. A. **109**:1537 (Nov. 6) 1937. Hagebusch, O. E.: Necropsies of Four Patients Following Administration of Elixir of Sulfanilamide-Massengill, ibid. **109**:1537 (Nov. 6) 1937. Lynch, K. M.: Diethylene Glycol Poisoning in the Human, South. M. J. **31**:134, 1938.

The principal pathologic changes were in the kidneys and liver.[95] The former showed chemical nephrosis, with enlargement, the development of cortical necrosis and hydropic degeneration of the epithelium of the convoluted tubules. The liver was enlarged and was described as tawny, although not bile stained, with pale, soft surfaces which bulged after sectioning. Sections showed extensive focal central hydropic degeneration of the hepatic cells without any marked inflammatory reaction.

Chemical analysis indicated that the preparation was essentially a 10 per cent solution of sulfanilamide in 72 per cent diethylene glycol.[96] Pharmacologic analysis[97] showed that the chief toxic agent in this elixir of sulfanilamide was the diethylene glycol and not the sulfanilamide. In fact, the characteristic pathologic lesions in the liver and spleen could not be produced by administration of sulfanilamide alone.

Clinical observation of patients receiving sulfanilamide has indicated that the most frequent toxic effect is the development of cyanosis.[98] This usually is mild and disappears rapidly after withdrawal of the drug.

Harvey and Janeway, Kohn, and Jennings and Southwell-Sanders[99] were among the first to report the occasional development of severe hemolytic anemia in association with sulfanilamide therapy. This anemia is readily controlled by withdrawal of the drug and the giving of a transfusion. In a few cases, as reported by Ottenberg and by Lockwood, Coburn and Stokinger[100] and in 1 case observed by us,

95. Cannon, P. R.: Pathologic Effects Following the Ingestion of Diethylene Glycol, Elixir of Sulfanilamide-Massengill, "Synthetic" Elixir of Sulfanilamide and Sulfanilamide Alone, J. A. M. A. **109**:1536 (Nov. 6) 1937.

96. Schoeffel, E. W.; Kreider, H. R., and Peterson, J. B.: Chemical Examination of Elixir of Sulfanilamide-Massengill, J. A. M. A. **109**:1532 (Nov. 6) 1937.

97. Geiling, E. M. K.; Coon, J. M., and Schoeffel, E. W.: Preliminary Report of Toxicity Studies on Rats, Rabbits, and Dogs Following Ingestion in Divided Doses of Diethylene Glycol, Elixir of Sulfanilamide-Massengill, and "Synthetic" Elixir, J. A. M. A. **109**:1532 (Nov. 6) 1937. Geiling, E. M. K., and Cannon, P. R.: Pathologic Effects of Elixir of Sulfanilamide (Diethylene Glycol) Poisoning: A Clinical and Experimental Correlation; Final Report, ibid. **111**:919 (Sept. 3) 1938.

98. Descombe, G.: Sulfhemoglobinemia Following Sulfanilamide Treatment, Lancet **1**:626, 1937.

99. Harvey, A. M., and Janeway, C. A.: The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide (Para-Aminobenzenesulfonamide), J. A. M. A. **109**:12 (July 3) 1937. Kohn, S. E.: Acute Hemolytic Anemia During Treatment with Sulfanilamide, ibid. **109**:1005 (Sept. 25) 1937. Jennings, G. M., and Southwell-Sanders, G.: Anemia and Agranulocytosis During Sulfanilmaide Therapy, Lancet **2**:898, 1937.

100. Lockwood, J. S.; Coburn, A. F., and Stokinger, H. E.: Studies on the Mechanism of the Action of Sulfanilamide: I. The Bearing of the Character of the Lesion on the Effectiveness of the Drug, J. A. M. A. **111**:2259 (Dec. 17) 1938.

the hemolytic anemia was sufficiently rapid in onset and marked in intensity to produce associated acute hemolytic jaundice. Fortunately, all these patients recovered without untoward incident.

Jaundice as a result of toxic hepatitis is an equally rare complication of sulfanilamide therapy. Hageman and Blake,[101] Saphirstein[102] and Long[103] have each reported a case of acute hepatitis. Garvin[104] has reported 5 cases with 1 death. Bannick, Brown and Foster[105] have reported 2 fatal cases, while Cline[106] has reported a case of acute yellow atrophy of the liver following sulfanilamide medication. We have observed 2 similar cases and a third which ended fatally but in which the lapse of a month between the administration of sulfanilamide and the development of jaundice made it difficult to determine the relation of the drug to the final outcome.

One of us observed another patient who while under treatment with sulfanilamide for hemolytic streptococcic septicemia suddenly showed severe jaundice. This therapy was discontinued, but the patient died within five days. At necropsy the liver was markedly enlarged, smooth and engorged. There was no extrahepatic obstruction of the biliary tract. Microscopic examination revealed focal periportal degeneration without leukocytic infiltration. The pathologic picture was that of acute toxic hepatitis. Chemical examination of the hepatic tissue showed 6 mg. of sulfanilamide per hundred grams as against a concentration of 1 to 1.5 mg. per hundred grams in tissue from the lungs. This single case suggests a specific affinity of sulfanilamide for the liver. It is by no means certain that the death described was directly due to sulfanilamide, but a contributory role is evident.

The majority of toxic manifestations which appear in the course of treatment with sulfanilamide apparently develop on the basis of sensitivity or idiosyncrasy. The cases that have just been cited indicate

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101. Hageman, P. O., and Blake, F. G.: A Specific Febrile Reaction to Sulfanilamide: Drug Fever, J. A. M. A. **109**:642 (Aug. 28) 1937.

102. Saphirstein, H.: Hepatitis and Toxic Erythemia with Desquamation Due to Sulfanilamide, Urol. & Cutan. Rev. **42**:101, 1938.

103. Long, P. H.: The Clinical Use of Sulfanilamide and Its Derivatives, with Special Reference to Their Possible Toxic Effects, Ohio State M. J. **34**: 977, 1938.

104. Garvin, C. F.: Toxic Hepatitis Due to Sulfanilamide, J. A. M. A. **111**: 2283 (Dec. 17) 1938.

105. Bannick, E. F.; Brown, A. E., and Foster, F. P.: Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds: Further Clinical Observations, J. A. M. A. **111**:770 (Aug. 27) 1938.

106. Cline, E. W.: Acute Yellow Atrophy of the Liver Following Sulfanilamide Medication, J. A. M. A. **111**:2384 (Dec. 24) 1938.

that, while such manifestations are infrequent, nevertheless there are cases in which sulfanilamide is capable of causing severe hepatic damage.

There is evidence that sulfanilamide, instead of being harmful, may in selected cases be of value in the treatment of infections of the liver and biliary tract. We have found, as have Ottenberg and Berck [107] and Crile,[108] that sulfanilamide is excreted in the bile after oral administration. Ottenberg and Berck also reported 2 cases of suppurative pylephlebitis and hepatic abscess in which recovery followed sulfanilamide therapy. In view of the almost hopeless character of such conditions, the further trial of this type of therapy is desirable.

VITAMIN K AND BLOOD COAGULATION

Clotting is the most striking and best known property of blood, but there is little agreement among physiologists as to the mechanism of this phenomenon. The available evidence indicates that the clotting of blood apparently involves two consecutive reactions. The first is the interaction between the prothrombin in the plasma, calcium and platelets (or tissue extract) to form thrombin. The second is the reaction between thrombin and fibrinogen with the formation of fibrin. Any attempt at further analysis of this phenomenon, as pointed out in the recent reviews of Howell [109] and Eagle,[110] leads the investigator into a maze of contradictory and often mutually exclusive theories.

The bleeding tendency which may develop in the patient with jaundice has long been recognized. The explanation, on the other hand, has been a source of controversy, as is demonstrated by the historical summaries presented by Moss;[111] Lewisohn;[112] Judd, Snell and Hoerner;[113] Ivy, Shapiro and Melnick,[114] and others. It is now accepted that the resorption of bile is without direct effect on the

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107. Ottenberg, R., and Berck, M.: Sulfanilamide Therapy for Suppurative Pylephlebitis and Liver Abscess, J. A. M. A. **111**:1374 (Oct. 8) 1938.

108. Crile, G., Jr.: Recent Advances in the Treatment of Obstructive Jaundice, Cleveland Clin. Quart. **6**:116, 1939.

109. Howell, W. H.: Theories of Blood Coagulation, Physiol. Rev. **15**:435, 1935.

110. Eagle, H.: Recent Advances in the Blood Coagulation Problem, Medicine **16**:138, 1937.

111. Moss, W.: Experimental Obstructive Jaundice: Its Effect on Fibrinogen and Coagulation of the Blood, Arch. Surg. **26**:1 (Jan.) 1933.

112. Lewisohn, R.: Haematologic Studies as a Basis for Determining the Risk of Post-Operative Hemorrhage in Jaundice Patients, Ann. Surg. **94**:80, 1931.

113. Judd, E. S.; Snell, A. M., and Hoerner, M. T.: Transfusion for Jaundiced Patients, J. A. M. A. **105**:1653 (Nov. 23) 1935.

114. Ivy, A. C.; Shapiro, P. F., and Melnick, P.: The Bleeding Tendency in Jaundice, Surg., Gynec. & Obst. **60**:781, 1935.

coagulation of the blood. The concentration of bilirubin, bile salts or cholesterol in the blood in jaundice bears no relation to the disturbance in the coagulability of the blood. Calcium deficiency, if present, ordinarily does not determine the tendency toward hemorrhage. The amount of fibrinogen, as shown by Lewisohn,[112] Ham and Curtis,[115] Moss and others, is rarely diminished in jaundice. Barlik [116] postulated the presence of interfering substances in the nature of antithrombin or antiprothrombin; and Carr and Foote [117] tried to characterize them chemically, but this work has not been confirmed. Howell suggested that heparin may be responsible for the normal fluidity of the blood; but this view is not accepted, and thus far there has been no evidence indicating an increase in the concentration of heparin in the blood in jaundice.

Recent investigators have agreed that a decrease in the amount of prothrombin in the plasma is the most probable explanation of the hemorrhagic tendency in jaundice. This was suggested by the studies of Lewisohn; Bancroft, Kugelmass and Stanley-Brown; [118] Nygaard; [119] and Quick, Stanley-Brown and Bancroft [120] and has been confirmed by Warner, Brinkhous, and Smith; [121] Boyce and McFetridge; [122] Quick,[123] and others in cases of jaundice.

Slight reductions in the prothrombin content of the blood have little effect on the coagulation of blood. The coagulation time, as measured by the usual methods, shows but little increase until more than 80 per cent of the prothrombin is lost. Any reduction below this critical

115. Ham, T. H., and Curtis, F. C.: Plasma Fibrinogen Response in Man: Influence of the Nutritional State, Induced Hyperpyrexia, Infectious Disease and Liver Damage, Medicine **17**:413, 1938.

116. Barlik, A.: Ueber das Wesen der verzögerten Blutgerinnung beim Stauungsikterus, Arch. f. klin. Chir. **176**:252, 1933.

117. Carr, J. L., and Foote, F. S.: Progressive Obstructive Jaundice: Changes in Certain Elements of the Blood and Their Relation to Coagulation, Arch. Surg. **29**:277 (Aug.) 1934.

118. Bancroft, F. W.; Kugelmass, N., and Stanley-Brown, M.: Evaluation of Blood Clotting Factors in Surgical Disease, Ann. Surg. **90**:161, 1929.

119. Nygaard, K. K.: Coagulability of Blood Plasma: A Method of Determining the Hemorrhagic Tendency of Jaundiced Patients, Proc. Staff Meet., Mayo Clin. **7**:691, 1932.

120. Quick, A. J.; Stanley-Brown, M., and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and Jaundice, Am. J. M. Sc. **190**:501, 1935.

121. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**:667, 1936.

122. Boyce, F. F., and McFetridge, E. M.: A Serum Volume Test for the Hemorrhagic Diathesis in Jaundice, J. Lab. & Clin. Med. **23**:202, 1937.

123. Quick, A. J.: The Nature of the Bleeding in Jaundice, J. A. M. A. **110**: 1658 (May 14) 1938.

level, on the other hand, is accompanied by a marked disturbance in the clotting mechanism. This observation explains why a patient with prothrombin deficiency may show no tendency to hemorrhage before operation, but when the prothrombin content of the blood is further reduced by the trauma of operation, the hemorrhagic tendency may become manifest in fatal form. Fortunately, the converse is also true, and only a slight increase in the prothrombin content of the blood may suffice to control the hemorrhagic tendency. The beneficial effects of transfusion probably are to be explained on such a basis.

Not only do patients with jaundice show a reduction in the prothrombin content of the blood, but Smith, Warner and Brinkhous [124] and Quick have found that similar changes occur in experimental animals after injury to the liver from chloroform or carbon tetrachloride. Changes in the prothrombin content of the blood have also been noted independently of hepatic injury. Farmers have noted a hemorrhagic tendency in stock fed on sweet clover hay which has been spoiled during curing. Roderick [125] noted that there was prothrombin deficiency in this condition; his investigations have been extended by Quick.[126]

Dam and Schønheyder [127] in Denmark and Almquist and Stokstad [128] in this country discovered that a hemorrhagic disease could be produced in chicks by means of a diet deficient in a new food accessory. Dam named this the "koagulation vitamin" or vitamin K. Dam and his co-workers [129] and later Quick found that the blood of chicks suffering from a deficiency of vitamin K was deficient in prothrombin. Feeding of vitamin K in the form of green vegetables, extracts of

124. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), J. Exper. Med. **66**:801, 1937.

125. Roderick, L. M.: A Problem in the Coagulation of the Blood: Sweet Clover Disease of Cattle, Am. J. Physiol. **96**:413, 1913. Roderick, L. M., and Schalk, A. F.: Studies on Sweet Clover Disease, Bulletin, North Dakota Agricultural Experiment Station, 1931.

126. Quick, A. J.: The Coagulation Defect in Sweet Clover Disease and in the Hemorrhagic Chick Disease of Dietary Origin, Am. J. Physiol. **118**:260, 1937.

127. Dam, H., and Schønheyder, F.: A Deficiency Disease in Chicks Resembling Scurvy, Biochem. J. **28**:1355, 1934; The Occurrence and Chemical Nature of Vitamine "K," ibid. **30**:897, 1936.

128. Almquist, H. J., and Stokstad, E. L. R.: Hemorrhagic Chick Disease of Dietary Origin, J. Biol. Chem. **11**:105, 1935.

129. Dam, H.: The Antihemorrhagic Vitamin of the Chick, Biochem. J. **29**: 1273, 1935. Schønheyder, F.: The Quantitative Determination of Vitamin K, ibid. **30**:890, 1936. Dam, H.; Schønheyder, F., and Tage-Hansen, E.: Studies on the Mode of Action of Vitamin K, ibid. **30**:1075, 1936. Dam, H., and Schønheyder, F.: Vitamin K, Nord. med. tidskr. **12**:1097, 1936.

alfalfa, fish meal or several vegetable oils cured the hemorrhagic tendency in chicks and restored the prothrombin value to normal.

Almquist,[130] Almquist and Stokstad[131] and Ansbacker[132] have reported attempts to secure concentrated preparations of vitamin K, and Thayer and his associates[133] have reported the isolation of a crystalline product from alfalfa leaves that is very active in restoring the clotting time of the blood of hemorrhagic chicks to normal. Lichtman and Chambers[134] more recently have reported the isolation of an active clotting factor from the liver.

In 1936 Greene[1b] discussed the importance of bile for the absorption of fats and of vitamin A. Since then Greaves and Schmidt[135] have published a series of reports indicating the importance of bile to the absorption of the various fat-soluble vitamins, carotene and vitamins D and E. Hawkins and Whipple[136] reported the development of a hemorrhagic tendency in dogs with an experimentally produced biliary fistula. Hawkins and Brinkhous[137] and Greaves and Schmidt[138] showed that this was due to a deficiency of prothrombin in the blood. It can be corrected by feeding either bile or vitamin K. Similar results have been reported in experimental obstructive jaundice.

130. Almquist, H. J.: Purification of the Antihemorrhagic Vitamin, J. Biol. Chem. **114**:241, 1936; Chemical and Physical Studies on the Antihemorrhagic Vitamin, ibid. **117**:517, 1937; Further Studies on the Antihemorrhagic Vitamin, ibid. **120**:635, 1937.

131. Almquist, H. L., and Stokstad, E. L. R.: Factors Influencing the Incidence of Dietary Hemorrhagic Disease in Chicks, J. Nutrition **12**:329, 1936.

132. Ansbacker, S.: New Observations on the Vitamin K Deficiency of the Chick, Science **88**:221, 1938.

133. Thayer, S. A.; MacCorquodale, D. W.; Binkley, S. B., and Doisy, E. A.: The Isolation of a Crystalline Compound with Vitamin K Activity, Science **88**: 243, 1938.

134. Lichtman, A. L., and Chambers, W. H.: Reduced Blood Coagulation Time by the Injection of Sterol Extract of Liver, Science **88**:358, 1938.

135. Greaves, J. D., and Schmidt, C. L. A.: Rôle Played by Bile in Absorption of Vitamin D in the Rat, J. Biol. Chem. **102**:101, 1933; Studies on the Vitamin A Requirements of the Rat, Am. J. Physiol. **116**:456, 1936; Relation of Certain Bile Acids to the Absorption of Beta-Carotene in the Rat, Proc. Soc. Exper. Biol. & Med. **36**:434, 1937; Relation of Bile to Absorption of Vitamin E in the Rat, ibid. **37**:40, 1937.

136. Hawkins, W. B., and Whipple, G. H.: Bile Fistulas and Related Abnormalities, Bleeding, Osteoporosis, Cholecystitis and Duodenal Ulcer, J. Exper. Med. **62**:599, 1935.

137. Hawkins, W. B., and Brinkhous, K. M.: Prothrombin Deficiency the Cause of Bleeding in Bile Fistula Dogs, J. Exper. Med. **63**:795, 1936.

138. Greaves, J. D., and Schmidt, C. A. L.: Nature of the Factor Concerned in the Loss of Blood Coagulability of Bile Fistula Rats, Proc. Soc. Exper. Biol. & Med. **37**:43, 1937. Greaves, J. D.: The Nature of the Factor Which Is Concerned in the Loss of Blood Coagulability of Bile Fistula and Jaundiced Rats. Am. J. Physiol. **125**:423, 1939.

Clinical and experimental evidence therefore is in agreement that the hemorrhagic tendency seen in cases of obstructive jaundice or of biliary fistula is related to a deficiency of prothrombin in the blood. The maintenance of a normal prothrombin value is determined by the presence in the food of an adequate supply of vitamin K and in the bowel of sufficient bile to insure the proper absorption of vitamin K. The role of the liver is less well understood, though the prothrombin content of the blood is decreased after experimental hepatic injury and in some cases of cirrhosis and severe hepatitis.

The clinical application of these findings has been made in a number of laboratories. Preparations of bile or bile salts [139] as well as viosterol were administered to jaundiced patients empirically with occasional benefit before the role of either prothrombin or vitamin K was understood.

Extracts of fish meal or alfalfa or other substances rich in vitamin K have been administered to jaundiced patients with consequent increase in the prothrombin content of the blood and reduction in the hemorrhagic tendency. Warner, Brinkhous and Smith; [140] Butt, Snell and Osterberg; [141] Dam and Glavind; [142] Brinkhous, Smith and Warner; [143] Snell, Butt and Osterberg; [144] Ravdin; [145] Walters, [146] and Olson and Menzel [147] agree that the oral administration of vitamin K and bile salts in both the preoperative preparation and the postoperative care

139. McNealy, R. W.; Shapiro, P. F., and Melnick, P.: The Effect of Viosterol in Jaundice, Surg., Gynec. & Obst. **60**:785, 1935. Johnson, C. G.: Preoperative and Post-Operative Treatment of Cases of Obstructive Jaundice, Surgery **3**:875, 1938.

140. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: Bleeding Tendency of Obstructive Jaundice: Prothrombin Deficiency and Dietary Factors, Proc. Soc. Exper. Biol. & Med. **37**:628, 1938.

141. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: The Use of Vitamin K and Bile in Treatment of the Hemorrhagic Diathesis in Cases of Jaundice, Proc. Staff Meet., Mayo Clin. **13**:74, 1938.

142. Dam, H., and Glavind, J.: Vitamin K in Human Pathology, Lancet **1**: 720, 1938.

143. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula: Effect of Feeding Bile and Alfalfa (Vitamin K), Am. J. M. Sc. **196**:50, 1938.

144. Snell, A. M.; Butt, H. R., and Osterberg, A. E.: Treatment of the Hemorrhagic Tendency in Jaundice with Especial Reference to Vitamin K, Am. J. Digest. Dis. **5**:590, 1938.

145. Ravdin, I. S., in discussion on Snell, Butt and Osterberg.[144]

146. Walters, W.: Lesions of the Extrahepatic Biliary Tract, J. A. M. A. **11**:2477 (Dec. 31) 1938.

147. Olson, K. B., and Menzel, H.: The Bleeding Tendency in Obstructive Jaundice and Its Control by Means of Vitamin K, Surgery, to be published.

of jaundiced patients is effective in preventing and controlling the hemorrhagic diathesis of these patients.

This procedure, while largely empiric, nevertheless represents a real therapeutic advance and deserves a more intensive clinical use. Snell, Butt and Osterberg have recommended the oral administration of 1 to 4 Gm. of animal bile salts and 0.4 to 1.2 Gm. of alfalfa concentrate daily. Olson and Menzel used 4 Gm. of bile salts and 1,000 units of vitamin K daily for from two to seven days.

At present the commercially available preparations of vitamin K must be given orally or administered through a duodenal tube, as they are not suitable for parenteral administration. Dam and his associates [148] have reported the successful intramuscular use of purified concentrate of vitamin K, but Butt, Snell and Osterberg [149] found that their preparations were not as effective in reducing the prothrombin time after intramuscular injection as was the same quantity given by mouth. When crystalline preparations of vitamin K become available, it may be possible to develop efficacious methods of parenteral administration.

The past year has seen the introduction of "blood banks" in many hospitals [150] in this country. "Bank blood" which has been stored for three to ten days is satisfactory for transfusion in the great majority of cases. Rhoads and Panzer [151] and Olson and Menzel have recently demonstrated that there is a rapid fall in the prothrombin content of "bank blood." These reports, while not substantiated by clinical cases, nevertheless imply that after the first day or so "bank blood" would be of little value in overcoming the bleeding tendency of the jaundiced patient. Earlier surgical experience, as summarized by Judd, Snell and Hoerner, indicated that transfusion was the most effective method then available of controlling this tendency to bleeding. The recent work on the prothrombin content of the blood has indicated that the improvement following transfusion is short lived and much inferior to the effect produced by the administration of preparations of vitamin K

148. Dam, H., and Glavind, J.: The Clotting Power of Human and Mammalian Blood in Relation to Vitamin K, Acta med. Scandinav. **96**:108, 1938. Dam, H.; Glavind, J.; Lewis, L., and Tage-Hansen, E.: Studies on the Mode of Action of Vitamin K, Scandinav. Arch. f. Physiol. **79**:121, 1938.

149. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: Further Observations on the Use of Vitamin K in the Prevention and Control of the Hemorrhagic Diathesis in Cases of Jaundice, Proc. Staff Meet., Mayo Clin. **13**:753, 1938.

150. Fantus, B., and Schirmer, E. H.: The Therapy of the Cook County Hospital: Blood Preservation Technic, J. A. M. A. **111**:317 (July 23) 1938. Cameron, C. S., and Ferguson, L. K.: The Operation and Technique of the Blood Bank at the Philadelphia General Hospital, Surgery **5**:237, 1939.

151. Rhoads, J. E., and Panzer, L. M.: The Prothrombin Time of "Bank Blood," J. A. M. A. **112**:309 (Jan. 28) 1939.

and bile salts. In consequence, the number of transfusions given for the control of the hemorrhagic tendency in jaundiced patients is likely to be reduced markedly in the future.

SPHEROCYTIC JAUNDICE

Diseases of the spleen are of especial interest to both internist and surgeon because of the position of this organ as an integral part of the hemopoietic system, on the one hand, and its association with the liver on the other. Hemolytic jaundice is an example of a condition in which both these relations of the spleen are affected.

A special clinic for the study of splenopathies was organized at the Columbia Medical Center [152] several years ago, and the investigators have begun to report on the results of their studies.

Thompson,[153] as part of this study of 55 cases of hemolytic jaundice, has pointed out that the term hemolytic jaundice is used clinically in all cases in which there is evidence of jaundice and anemia due to increased destruction of the red blood cells. The spleen usually is enlarged and the number of reticulocytes in the blood increased. Thompson, however, has reemphasized the fact that cases of this clinical syndrome should be divided into two separate groups.

Minkowski [154] was the first to establish congenital hemolytic jaundice as a clinical entity. Chauffard,[155] in 1907, discovered the markedly increased fragility of the erythrocytes in hypotonic salt solution and a year later reported the presence of reticulated red blood cells in large numbers.[156] Haden [157] further demonstrated that the microcytosis was due to the presence in the blood of a variable proportion of spherical erythrocytes which were smaller in diameter than normal. It is these smaller cells which are alone responsible for the fragility in this condition. This spherocytosis apparently represents a congenital defect in the red blood cells. Krumbhaar [158] therefore has suggested the term spherocytic jaundice for this condition.

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152. Whipple, A. O.: The Medical-Surgical Splenopathies, Bull. New York Acad. Med. **15**:174, 1939.

153. Thompson, W. P.: Hemolytic Jaundice: Its Diagnosis, Behavior and Treatment, Bull. New York Acad. Med. **15**:177, 1939.

154. Minkowski, O.: Ueber eine hereditäre, unter dem Bilde eines chronischen Icterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affection, Verhandl. d. deutsch. Kong. f. inn. Med. **18**:316, 1900.

155. Chauffard, A.: Pathogénie de l'ictère congénital de l'adulte, Semaine méd. **27**:25, 1907.

156. Chauffard, A.: Les ictères hémolytiques, Semaine méd. **28**:49, 1908.

157. Haden, R. L.: Mechanism of Increased Fragility of Erythrocytes in Congenital Hemolytic Jaundice, Am. J. M. Sc. **188**:441, 1934.

158. Krumbhaar, E. B.: Modern Concepts of Anemia from the Clinical Standpoint, Bull. New York Acad. Med. **13**:501, 1937.

Summarizing the knowledge of this condition, Thompson has pointed out that it is a chronic disease of long duration and relative mildness, though acute exacerbations may occur. The presenting symptom is usually chronic variable jaundice. Splenomegaly is the outstanding feature on physical examination. Anemia may be mild or severe, and in cases of latent spherocytic jaundice the blood count may be normal. The degree of jaundice and the degree of reticulocytosis are both variable but tend to be proportional to the degree of anemia. The peripheral blood contains spherocytes, which may be recognized directly and counted by examination of wet film preparations or measured indirectly by determination of the fragility in hypotonic salt solution.

Spherocytes constitute 10 to 25 per cent of the total number of erythrocytes. They not only are present in the blood of all patients with clinically recognizable forms of the disease but may also be found in their relatives in whom the condition is latent. These spherical cells are selectively removed from the circulation by the spleen. That they are actively destroyed there is suggested by the observation of Kaznelson,[159] Rich and Rienhoff,[160] Greene and Conner,[161] and Thompson that in these cases blood from the splenic vein contains more bilirubin than blood from the splenic artery.

Indirect evidence of the activity of the spleen in destruction of these cells is afforded by the rapid disappearance both of the jaundice and of the evidence of increased hemolysis following splenectomy. That the spherocytes persist in the blood in undiminished numbers after splenectomy is further evidence that the beneficial effect of splenectomy is due to the cessation of a hemolytic process and not to the return of erythropoiesis to normal.

Transfusion is the accepted method of treatment for the anemia associated with spherocytic jaundice,[162] especially during a hemoclastic

159. Kaznelson, P.: Beitrag zur Entstehung des hemolytischen Ikterus, Wien. Arch. f. inn. Med. **1**:563, 1920.

160. Rich, A. R., and Rienhoff, W. F., Jr.: The Bile-Pigment Content of the Splenic Vein, Bull. Johns Hopkins Hosp. **36**:431, 1925.

161. Greene, C. H., and Conner, H. M.: Diseases of the Liver: V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, Arch. Int. Med. **38**:167 (Aug.) 1926.

162. Tileston, W.: Hemolytic Jaundice, Medicine **1**:355, 1922. Cheney, W. F., and Cheney, G.: Chronic Hereditary Jaundice, Am. J. M. Sc. **187**:191, 1934. Bazin, A. T.: Splenectomy: Operative Procedure and After-Care, Canad. M. A. J. **33**:482, 1935. Hurxthal, L. M.: Hemolytic Jaundice: Consideration of the Diagnosis and Treatment, S. Clin. North America **15**:1475, 1935. Dudley, G. S.: Familial Hemolytic Jaundice, ibid. **16**:839, 1936.

crisis and immediately before splenectomy. Lord Dawson [163] and Hartfall and Stewart [164] have reported cases in which a fatal reaction occurred after a transfusion. Baker and Dodds,[165] Wise [166] and Sharpe and Davis [167] have reported severe reactions in patients who were given a transfusion while in a state of acute hemoclastic crisis. Doan, Wiseman and Erf [168] are of the opinion that a transfusion, with the addition of red blood cells, only furnishes more material for hemolysis, with further pigmentary and toxic embarrassment to both the liver and the kidneys. Dawson concluded that the reaction and subsequent deaths in his cases were due to blocking of the renal tubules with masses of acid hematin pigment.

DeGowin, Osterhagen and Andersch [169] have given a clue to the prevention of such a reaction by their experimental studies on dogs in which they found that hemoglobin was innocuous in large amounts when the urine was alkaline but was precipitated in the renal tubules when the urine was acid. Witt [170] has practiced alkalization of the urine in such cases before transfusion. From these findings it appears that transfusion in the presence of a severe hemoclastic crisis is dangerous and to be avoided. Should transfusion be considered imperative, thorough alkalization of the urine may prevent a severe reaction or a fatality.

In marked contrast to the cases of spherocytic jaundice are the cases of atypical hemolytic jaundice. The condition may be acquired as the result of the administration of specific toxic substances, as in the cases of acute hemolytic jaundice associated with sulfanilamide therapy which have been discussed. There are also cases of idiopathic jaundice in which, as Thompson has pointed out, the mechanism is not understood at present and in which splenectomy is of no benefit.

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163. Dawson, B. E.: Hemolytic Jaundice, Brit. M. J. **1**:921 and 963, 1931.

164. Hartfall, S. J., and Stewart, M. J.: Massive Paravertebral Heterotopia of Bone-Marrow in a Case of Acholuric Jaundice, J. Path. & Bact. **37**:455, 1933.

165. Baker, S. L., and Dodds, E. C.: Obstruction of the Renal Tubules During the Excretion of Hemoglobin, J. Path. & Bact. **6**:247, 1925.

166. Wise, W. D.: Hemolytic Jaundice, Am. J. Surg. **20**:722, 1933.

167. Sharpe, J. C., and Davis, H. H.: Severe Reactions Following Transfusions in Hemolytic Jaundice, J. A. M. A. **110**:2053 (June 18) 1938.

168. Doan, C. A.; Wiseman, B. K., and Erf, L. A.: Studies in Hemolytic Jaundice, Ohio State M. J. **30**:493, 1934.

169. DeGowin, E. L.; Osterhagen, H. F., and Andersch, M.: Renal Insufficiency from Blood Transfusion: Relation to Urinary Acidity, Arch. Int. Med. **59**:432 (March) 1937; Grave Sequels to Transfusion: Clinical Study of Thirteen Cases Occurring in Three Thousand and Five Hundred Transfusions, Ann. Int. Med. **11**:1777, 1938.

170. Witt, L. J.: A Note on Blood Transfusions, Lancet **1**:1297, 1929.

CIRRHOSIS OF THE LIVER

During the past year Bloomfield [171] has had occasion to survey the natural history of chronic hepatitis and to reemphasize that cirrhosis of the liver usually is the terminal stage of chronic hepatitis of long duration. This conception is not new, but it usually has not been emphasized or the evidence on which it rests has not been, as here, brought forward in "a round unvarnished tale." He has pointed out in his study of 41 cases that the early course of the disease usually is run without clinical symptoms. Only about 10 per cent of his patients gave a history of a previous attack of jaundice, so that he concluded that acute hepatitis with jaundice rarely is the initial stage or precursor of cirrhosis. That latent hepatitis may exist for long periods without concomitant symptoms was shown by 2 patients in each of whom a firm, enlarged liver and splenomegaly were incidental discoveries. These patients continued to be free from symptoms for several years but finally died with the characteristic clinical picture of portal cirrhosis nine and eleven years, respectively, after the first examination.

In 3 cases the clinical history suggested that the process began with an initial attack of acute hepatitis which ran a rapid progressive course, with the development of the picture of cirrhosis within a few months. In a considerable number of cases, however, it was impossible to decide whether the patient was first seen because of acute hepatitis or because of an acute exacerbation occurring in the course of a chronic and previously latent hepatitis.

These cases reported by Bloomfield therefore lend support to the idea that hepatic cirrhosis represents the end stage of chronic hepatitis, with progressive injury to the liver either from a chronic, slowly progressive disease or from the effect of repeated exacerbation of such a disease. This idea is in harmony with the experimental finding, noted in the review of Moon,[172] that the histologic picture of cirrhosis may be produced in animals by the repeated administration over a prolonged period of such hepatotoxins as carbon tetrachloride, copper and phosphorus.

Recent experimental studies have emphasized the importance of diet in relation to the symptoms of cirrhosis. Bollman [173] has reported the daily administration of carbon tetrachloride to a series of dogs on differ-

171. Bloomfield, A. L.: The Natural History of Chronic Hepatitis (Cirrhosis of the Liver), Am. J. M. Sc. **195**:429, 1938.

172. Moon, V. H.: Experimental Cirrhosis in Relation to Human Cirrhosis, Arch. Path. **18**:381 (Sept.) 1934; Experimentelle Lebercirrhose und ihre Beziehungen zur Aetiologie der menschlichen Cirrhose, Klin. Wchnschr. **13**:1489 and 1521, 1934.

173. Bollman, J. L.: Some Experimental Observations Pertinent to the Treatment of Hepatic Disease, Ann. Int. Med. **12**:1, 1938.

ent diets. The 4 animals receiving a diet of 80 per cent fat and 10 per cent each of carbohydrate and protein were all dead within three weeks. In each case the liver was enlarged and fatty and showed numerous areas of degeneration. Two of the animals which received only lean meat died within three months, and the other 2 had definite ascites. The dogs on diets of 50 per cent carbohydrate and 25 per cent each of fat and protein and the ones on diets with 90 per cent carbohydrate were in good condition six to eight months later.

Bollman further found that alcohol was without effect on the livers of dogs receiving a well balanced diet though given twice daily to the stage of intoxication for more than two years. In fasting animals or those on diets rich in fat the livers became fatty, and the administration of alcohol greatly increased the rapidity of this change. Animals with such fatty livers showed marked sensitization to the toxic effects of carbon tetrachloride.

The relation of the liver to the metabolism of fat and the extensive recent literature on experimental studies of fatty infiltration of this organ were reviewed in 1937. These studies originated in the observation of Fisher [174] and of Allan, Bowie, Macleod and Robinson [175] that depancreatized dogs treated with insulin in adequate dosage nevertheless had marked fatty infiltration of the liver which eventually resulted in death. Chaikoff, Connor and Biskind [176] have extended these observations and have shown that after four or five years the livers of these animals presented the picture of well advanced portal cirrhosis. They considered that the sequence of events was fatty infiltration, hyaline degeneration and atrophy of the cells at the periphery of the lobules and then orderly fibroblastic proliferations, ending with the typical appearance and fibrotic structure of cirrhosis.

The cause of the fatty infiltration of the liver in the depancreatized dog has been a source of controversy. It can be prevented by the feeding of raw pancreas. Best, Ferguson and Hershey [177] showed that it could be prevented by feeding lecithin or choline and consider that the latter is the active principle in the pancreas. Dragstedt, Van Prohaska and

174. Fisher, N. F.: Attempts to Maintain the Life of Totally Pancreatectomized Dogs, Am. J. Physiol. **67**:634, 1924.

175. Allan, F. N.; Bowie, D. J.; Macleod, J. J. R., and Robinson, W. L.: Behavior of Depancreatized Dogs Kept Alive with Insulin, Brit. J. Exper. Path. **5**:75, 1924.

176. Chaikoff, I. L.; Connor, C. L., and Biskind, G. R.: Fatty Infiltration and Cirrhosis of the Liver in Depancreatized Dogs Maintained with Insulin, Am. J. Path. **14**:101, 1938.

177. Best, E. H.; Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, J. Physiol. **79**:94, 1933.

Harms [178] prepared another extract from the pancreas, which they called the lipocaic hormone. When fed to dogs, this material prevented fatty infiltration of the liver. They consider that "lipocaic" is a specific hormone of the pancreas. The latter view has been denied by Best and Ridout,[179] who have insisted that the lipotropic effect of "lipocaic" in their hands could be explained by the lipotropic effect predicted from its choline and protein content. This subject is still a matter of controversy but serves to emphasize the importance of diet in its relation to fatty infiltration of the liver.

Connor [180] has continued the clinical application of these studies and has reviewed the literature dealing with fatty infiltration of the liver in its relation to the development of cirrhosis in diabetes and in chronic alcoholism. He has pointed out that

> Fatty infiltration of the liver occurs in those conditions where, because of lack of intake or absorption of food, fat is mobilized from the existing fat depots; and where, because of internal interference with the metabolism of fat due to anoxemia or tissue anoxia, the accumulated fat cannot be broken down for use. In the first instance it results from external starvation; in the second from what may be called internal or tissue starvation. In both instances normal carbohydrate-fat metabolism does not take place. Among the conditions in which this normal metabolism is altered or inhibited are the various diseases which, by their nature, are called wasting; the disease diabetes; and that following the introduction of poisons which inhibit proper tissue oxidation, the most common of which is alcohol . . .
>
> In the starvation accompanying progressive morbid states the condition is of little pathological importance, being in most cases terminal in nature. In diabetes the enlarged fatty liver may be influenced by insulin and by strict dieting, but also may persist for many years. In alcoholism a variety of factors operate to produce the same condition. Alcohol alone will cause some fatty infiltration, but as relative and sometimes absolute starvation is constantly associated with severe chronic alcoholism, the development of fatty infiltration of the liver most often depends on a combination of these two. The absence of vitamin B^1 in the diet may contribute to this also, but such deficiency is probably of minor importance . . . An analysis of existing recorded observations and experiments, indicate that a liver containing demonstrable neutral fat is in most cases pathological; that fat may pass into and out of the liver with astonishing rapidity; and that fat may be present in such amounts as to interfere seriously with both the metabolic and the mechanical functions of the organ . . . The development of perilobular fibrosis seems to be

178. Dragstedt, L. R.; Van Prohaska, J., and Harms, H. P.: Observations on a Substance in the Pancreas Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. **117**:175, 1936.

179. Best, C. H., and Ridout, J. H.: The Pancreas and the Deposition of Fat in the Liver, Am. J. Physiol. **122**:67, 1938.

180. Connor, C. L.: Fatty Infiltration of the Liver and the Development of Cirrhosis in Diabetes and Chronic Alcoholism, Am. J. Path. **14**:347, 1938; The Etiology and Pathogenesis of Alcoholic Cirrhosis of the Liver, J. A. M. A. **112**: 387 (Feb. 4) 1939.

the result of a combination of mechanical pressure, local tissue anoxia and general anoxemia, causing atrophy and degeneration of liver cells.

The alcoholic liver occurs in two forms, one of which is the precursor of the other. The first is the enlarged tense liver so swollen with fat that the distended surface lobules present the appearance of cirrhosis. This effect is further simulated by the intrahepatic block, which interferes with excretion of bile, and the transmission of portal blood. The clinical signs of jaundice and ascites are thus produced. Many such patients lapse into coma and die, and at autopsy the large liver is the only prominent finding. These show lobules distended with fat and some show, in addition, hyaline degeneration and atrophy of peripheral cells associated with early proliferation of fibroblasts.

A series of cases reported by Connor represented this form, and another series illustrated the second form, in which further proliferation of connective tissue produced the typical picture of portal cirrhosis as seen in chronic alcoholism. An unmistakable gradation of the one into the other is so manifest that the mechanism of the production of alcoholic cirrhosis seems to Connor to have been demonstrated. The absence of fat in many such livers at the end is explained by the exhaustion of body fat, by the discontinuance of the consumption of alcohol and by the resumption of a normal or a high carbohydrate diet.

Connor has further reported that from a study of a large number of cases composite pictures may be assembled to illustrate three phases of the disease of the liver produced by alcohol. The three phases occur at the ages of about 40 to 45, 50 to 55 and 50 to 65, respectively, the ages overlapping as would be expected from the nature of the disease. When it is understood that the first acute stage may be reached in from six months to two years, the second in from one to five years and the third in from two to twenty years or more, it can be seen how unreliable age statistics are. The age is usually above 40, because men usually do not begin to drink the quantity of alcohol necessary to produce these changes until after that age.

The acute fatty liver of alcoholism develops after the prolonged use of very large amounts of alcohol during which little or no food is taken or the food consists of protein and fat only. It is found in men picked up by the police who die shortly afterward in prison or in city hospitals. It is most common in the coroner's morgues in all large cities. When the patient lives long enough for clinical examination he may show signs of cirrhosis, such as jaundice and some ascites, but has a large liver. The liver is pale and greasy, containing about 60 per cent fat. It may be lobulated because of the severe swelling but is usually smooth. Because of the swelling there also may be intrahepatic obstruction of the bile ducts, giving a green coloration, and portal obstruction without fibrosis. Such livers are recognized by all medical examiners as evidence of alcoholism and as being associated generally with poor nutrition. The deaths of patients in this stage "represent the inevitable mortality

during the experimental production of cirrhosis in man." The others pass on to the next stage.

The fatty liver in which there is early but definite and progressing perilobular fibrosis is the product of alcoholism which is less in degree than that causing the first phase but which is nevertheless severe. In the liver which survives drastic alcohol poisoning and a partial starvation diet, a fibrous tissue stroma will develop in the course of time. The liver is large or of normal weight and moderately lobulated or smooth. It is sclerotic, it may not be bile stained and it produces classic early signs and symptoms of cirrhosis. The condition is the common fatty cirrhosis of the liver found in most classifications.

The liver in the third phase is likely to be somewhat reduced in size and to have a nodular surface and a thickened capsule. It never becomes as small as the liver of toxic cirrhosis, seldom weighing under 1,300 Gm. Fat may or may not be present. The condition follows the long-continued use of excessive amounts of alcohol by a person who has continued to take a better diet, but as to both alcohol and diet the habits have been abnormal. There may have been intermittent severe episodes of drinking lasting long enough to damage the liver permanently. To produce this condition requires much more than could be called a moderate use of alcohol, and it can be understood how by alternating the two primary factors involved, alcoholic intake and diet, the process may be accelerated or retarded indefinitely. This phase forms the classic cirrhosis of the portal type. Fat disappears from the liver when the body fat is exhausted, and the liver becomes smaller after prolonged starvation; fat rapidly disappears when the consumption of alcohol is discontinued, and the resumption of a normal diet or the administration of dextrose solution causes a rapid disappearance of fat as the liver fills with glycogen. The presence or absence of fat, then, has little significance in this late stage.

Connor has concluded that it is very doubtful whether in any person on a balanced diet alcoholic cirrhosis will develop. A person eating three regular, balanced meals a day will probably not become a chronic alcoholic addict, in the sense that this term is used here, as long as this regularity continues. It has been demonstrated in both man and experimental animals that it is possible to maintain metabolic equilibrium within safe limits even when large amounts of alcohol are taken habitually.

Less direct evidence for the relation of alcohol and cirrhosis was presented by Rowntree,[181] showing the reduction in the number of cases of cirrhosis observed in the United States after the passage of the

181. Rowntree, L. G.: Considerations in Cirrhosis of the Liver, J. A. M. A. **89**:1590 (Nov. 5) 1927.

National Prohibition Act. Evans and Gray [182] have recently reported statistics indicating that the incidence of cases of cirrhosis at the Los Angeles County Hospital has tripled since the repeal of the prohibition act.

The relation of fatty infiltration and alcoholism to the etiology of portal cirrhosis will not explain the genesis of all cases of cirrhosis. Many cases are noted in which the action of these two factors can be excluded specifically. Other specific causes of cirrhosis are known, but these studies have done much to clarify the old clinical impression that led to the use of the term "gin drinker's liver."

The emphasis on the importance of the associated diet likewise is significant. The regenerative and recuperative powers of the hepatic parenchyma are well known. Bollman has reported that he has not been able to produce cirrhosis in dogs by the administration of carbon tetrachloride to such an extent that ultimate symptomatic recovery was impossible when the administration of the drug was stopped. The time is yet to come when the clinician can make the same statement.

182. Evans, N., and Gray, P. A.: Laënnec's Cirrhosis: Report of Two Hundred and Seventeen Cases, J. A. M. A. **110**:1159 (April 9) 1938.

News and Comment

Industrial Health. — The twenty-fourth annual meeting of the American Association of Industrial Physicians and Surgeons with the American Conference on Occupational Diseases and Industrial Hygiene will be held at the Hotel Statler, Cleveland, June 5 to 8, 1939. A program of timely interest and importance will be presented by speakers of outstanding experience in all the medical and engineering problems involved in industrial health. Further information may be procured from A. G. Park, convention manager, 540 North Michigan Avenue, Chicago.

American Heart Association, Inc.—The fourteenth scientific sessions of the American Heart Association, Inc., will be held at the Hotel Jefferson, St. Louis, May 12 and 13, 1939. A general program is scheduled for the first day and a program for the study of the peripheral circulation on the second day.

Book Reviews

The Primate Thalamus. By A. Earl Walker, M.D. Price, $3. Pp. 321, with 96 illustrations. The University of Chicago Monographs in Medicine, Chicago: University of Chicago Press, 1938.

In this monograph Walker presents a comprehensive account of the anatomy, connections and function of the primate thalamus. A short historical introduction is followed by a detailed discussion of the gross and the nuclear structure of the thalamus of the macaque monkey, as typical of that found in the higher primates. In successive chapters consideration is given to the afferent connections of the thalamus, its relation to the cerebral cortex, the distribution of the projection fibers from the thalamic nuclei and geniculate bodies to the various cortical areas and the anatomic, physiologic and clinical significance of the thalamus. The author's extensive experiments, on which the book is based, were carried out entirely on the macaque monkey. The work was done at the University of Chicago, the University of Iowa, Yale University and the Laboratory of Neuropathology, Wilhelmina Gasthuis, in Amsterdam. The enormous literature on the thalamus is well summarized and woven into an orderly presentation of the whole.

In his study of the afferent connections of the thalamus, Walker utilized the Marchi technic to trace the centripetal degeneration following section of the spinal cord, destruction of the nuclei of the dorsal columns and section of the brachium conjunctivum. The projections of the thalamic nuclei to the cerebral cortex were studied by examining the retrograde degenerations in the nuclei by the Nissl method after decortication operations of varying extent. The results of these numerous experiments cannot be indicated here. In general, the intensity of the thalamic projection to the different cortical areas was found not to be uniform. The prefrontal cortex receives afferent fibers in great number from the nucleus medialis dorsalis, the motor cortex from the nucleus lateralis ventralis (which is the thalamic termination of fibers from the brachium conjunctivum) and the striate area of the occipital cortex from the lateral geniculate body. Walker has added considerable new information regarding the projection of the medial geniculate body, which receives afferent fibers from the cochlear nuclei of both sides. This portion of the metathalamus, he found, projects in an orderly fashion to a cytoarchitecturally unique "koniocortex," located in a small area on the superior surface of the first temporal convolution. The inferior portions of the temporal lobes, the greater part of the parietal lobules and the premotor areas receive only slight thalamic projections.

Three functionally distinct groups of nuclei may be recognized in the thalamus. The midline nuclei, constituting the first group, remain relatively constant throughout the mammalian scale and are present in primitive animals not possessing appendages. They appear to be concerned particularly with visceral sensibility. The second group—the nucleus ventralis posterior, the nucleus ventralis lateralis and the geniculate bodies—receive fibers from primary or secondary sensory neurons and project to the cerebral cortex. They develop phylogenetically with the elaboration of the limbs and with the appearance of the special senses of vision and audition. The third group—the nucleus lateralis posterior, the nucleus medialis dorsalis and the pulvinar—are of recent development; they do not receive afferent somatosensory fibers, but they do project to the cerebral cortex. They "appear to be related to the highest and most recently developed sensory modalities."

In this monograph Walker has summarized the present knowledge of the thalamus as the great substation which receives all sensory data from the environment and initiates their organization. In addition, he has contributed valuable

material from his own painstaking work and has furthered the knowledge in important respects. His book will aid the neurologist in understanding how the nervous system receives and organizes the sensory material out of which behavior is ultimately compounded. Although essentially a study in anatomy, this work will prove of interest and value to the neurophysiologist and to the clinician, who must understand the symptoms of neurologic disease. An extensive bibliography materially increases the usefulness of the book.

Diagnostics urgents: Abdomen. By H. Mondor. Third edition. Price, 210 francs. Pp. 1,120, with 248 illustrations. Paris: Masson & Cie, 1937.

What could be called the leitmotiv of this commendable work is the subscript to one of the illustrations: "Appendix of a little girl, operated upon, *thanks to her doctor* [italics not in text], for a gangrenous appendicitis which had not yet perforated." It is for the general practitioner that this book was written. The physician who has the privilege of first viewing the drama of the "acute abdomen" is the chief object of the author's efforts. He emphasizes, rightly, that the physician who must attend the patient with an acute abdominal condition in his home, deprived of instant access to a laboratory and consultations, bears a great responsibility. The victim's life is on a balance, with time measured in hours on the other pan. The diagnosis and the decision for surgical intervention must be made rapidly. The signs and symptoms which indicate the proper course toward relief and recovery are few and must be diligently sought and as expertly interpreted. It seems to the reviewer that this book offers as excellent a guide for such a search and for interpretation as could be expected.

The method of presentation is not dryly didactic. No speculation on pathogenesis, no detailed description of lesions and no discussion of therapeutics or of surgical technics are included. The dozen or so intra-abdominal disorders which demand prompt surgical treatment if the victim is to survive are the scope of the book. Much less attention is given to the nonsurgical diseases which simulate the "acute abdomen." The text is pleasantly written and is often almost journalistic in its terse economy of words. The author, surgeon to the Hôpital Bichat, illustrates his points with many case histories from his practice and from the experience and works of his colleagues. These histories are, in general, appropriate and are related in a manner more reminiscent of the "ward walk" than of the professorial lecture. Because the book is intended to be read by general practitioners and to simulate a personal conference, there is no formal bibliography, but many quotations, statistics and aphorisms of other surgeons are included and acknowledged.

Careful reading of this book should be valuable to any physician or student not only for the factual material but also for the highly idealistic and utilitarian attitude toward the grave problem of the "acute abdomen."

Heart Failure. By Arthur M. Fishberg, M.D., Associate in Medicine, Mount Sinai Hospital, New York. Cloth. Price, $8.50. Pp. 788, with 25 illustrations. Philadelphia: Lea & Febiger, 1937.

This book is rather unique in that it deals with heart disease only as it concerns heart failure. The various mechanisms leading to heart failure are discussed, as are also the circulatory changes that occur as a result of failure. In thus eliminating a discussion of heart disease other than that concerned with failure the author has been able to include a tremendous amount of information without making the book unduly large.

A consideration of the alterations of the circulation and the blood that are attendant on failure deals with blood volume, venous pressure, blood velocity, cardiac output and the other physiologic studies that have recently done much to help clear up the subject. Each of these subjects is generously dealt with, and the author has shown a nice discrimination in choosing those portions of the subjects that have a direct clinical application.

He then discusses the changes consequent on failure, such as dyspnea, edema, pulmonary engorgement and the like. This leads finally to a consideration of the heart itself, the mechanisms of failure and the accompanying dynamics of the circulation, always with a view to the clinical application of the material set forth.

There is an adequate discussion of the recent physiologic work that bears on the subject. The author gives his own views, together with the views of those with whom he is in agreement. In addition, he discusses current theories with which he disagrees and gives his reasons therefor.

Peripheral vascular failure, or shock, is definitely placed in its proper position as distinguished from heart failure.

While therapeutic measures are mentioned throughout the book as their rationale is developed—or as their use is contraindicated, treatment is again discussed in a separate section.

The author has shown his willingness to depart from old pathways when such departure has seemed justified. He offers a classification of heart failure which is helpful if not perfect. His attitude toward the importance of the coronary circulation in all forms of heart failure and his characterization of peripheral vascular failure are evidence of a flexibility of mind.

The student, the general practitioner or the cardiologist, if he seeks information relative to the failure of the circulation, will find it in this book.

Zur Entdeckung der Insulinschoktherapie bei akuten Geiteskrankheiten, insbesondere bei der Schizophrenie. By Dr. Julius Schuster. Price, 2 pengö. Pp. 90. Budapest: Druckerei der Pester Lloyd-Gesellschaft, 1938.

The author has apparently prepared this booklet to substantiate his claim for priority in discovering the usefulness of insulin in shock treatment of the psychoses. Priority, he says, is now falsely attributed to Sakel. By 1922 Schuster had arrived at the conclusion that mental disease could be favorably influenced by exceptionally large doses of insulin. The booklet includes brief abstracts of 30 case reports of various types of psychoses in which treatment with large doses of insulin was employed. The earliest of these records is dated January 1921. (Banting and Best announced the discovery of insulin in February 1922!)

Pages 15 to 65 are devoted to reviews of several phases of carbohydrate metabolism, and whenever possible these are discussed in relation to cerebral physiology. Schuster says that insulin acts in cases of psychoses by inducing "brain shock," which is related to protein shock and to the metabolism of protein, carbohydrate and fat.

Although the biochemical observations are interesting, the reader is not enlightened as to the mechanism by which hypoglycemia now "cures" psychoses.

Heart Disease in General Practice. By Paul D. White. In Fishbein, Morris: National Medical Monographs. Price, $3. Pp. 338, with 47 illustrations. New York: National Medical Book Co., Inc., 1937.

Using the method of questions and answers, Dr. White has produced a sort of catechism of heart disease. His wide experience in teaching and writing has made it possible for him to strip the subject of nonessentials, and the result is a really admirable summary of what one must know to deal intelligently with cardiac problems. It is hoped that the general physician will take advantage of this little book; only too often, misled by the propaganda of the pharmaceutic houses, he uses all sorts of complicated preparations of dubious value when only a few simple drugs are really needed.

It is to be regretted that this excellent book is printed on such poor paper, even though the price is low.